



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US98/11422</p> <p>(22) International Filing Date: 4 June 1998 (04.06.98)</p> <p>(30) Priority Data: 60/048,915 6 June 1997 (06.06.97) US 60/048,882 6 June 1997 (06.06.97) US (Continued on the following page)</p> <p>(71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): YOUNG, Paul [US/US]; 122 Beckwith Street, Gaithersburg, MD 20878 (US). GREENE, John, M. [US/US]; 872 Diamond Drive, Gaithersburg, MD 20878 (US). FERRIE, Ann, M. [US/US]; 13203 L Astoria Hill Court, Germantown, MD 20874 (US). RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). HU, Jing-Shan [CN/US]; 1247 Lakeside Drive #3034, Sunnyvale, CA 94086 (US). OLSEN, Henrik, S. [DK/US]; 182 Kendrick Place #24, Gaithersburg, MD 20878 (US). EBNER, Reinhard [DE/US]; 9906 Shelburne Terrace #316,</p>	<p>Gaithersburg, MD 20878 (US). BREWER, Laurie, A. [US/US]; 14920 Mt. Nebo Road, Poolesville, MD 20837 (US). MOORE, Paul, A. [GB/US]; Apartment 104, 1908 Holly Ridge Drive, McLean, VA 22102 (US). SHI, Yanggu [CN/US]; 437 West Side Drive, Gaithersburg, MD 20878 (US). FLORENCE, Charles [US/US]; (US). FLORENCE, Kimberly [US/US]; 12805 Atlantic Avenue, Rockville, MD 20851 (US). LAFLEUR, David, W. [US/US]; 1615 Q Street, N.W. #807, Washington, DC 20009 (US). NI, Jian [CN/US]; 5502 Manorfield Road, Rockville, MD 20853 (US). FAN, Ping [CN/US]; Apartment 302, 335 West Side Drive, Gaithersburg, MD 20878 (US). WEI, Ying-Fei [CN/US]; 13524 Straw Bale Lane, Darnestown, MD 20878 (US). FISCHER, Carrie, L. [US/US]; 5810 Hall Street, Burke, VA 22015 (US). SOPPET, Daniel, R. [US/US]; 15050 Stillfield Place, Centreville, VA 22020 (US). LI, Yi [CN/US]; 1247 Lakeside Drive #3034, Sunnyvale, CA 94086 (US). ZENG, Zhizhen [CN/US]; 13950 Saddleview Drive, Gaithersburg, MD 20878 (US). KYAW, Hla [MM/US]; 520 Sugarbush Circle, Frederick, MD 21703 (US). YU, Guo-Liang [CN/US]; 13524 Straw Bale Lane, Darnestown, MD 20878 (US). FENG, Ping [CN/US]; 4 Relda Court, Gaithersburg, MD 20878 (US). DILLON, Patrick, J. [US/US]; 1055 Snipe Court, Carlsbad, CA 92009 (US). ENDRESS, Gregory, A. [US/US]; 9729 Clagett Farm Drive, Potomac, MD 20854 (US). CARTER, Kenneth, C. [US/US]; 11601 Brandy Hall Lane, North Potomac, MD 20878 (US).</p> <p>(74) Agents: HOOVER, Kenley, K. et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 10850 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With declaration under Article 17(2)(a); without abstract; title not checked by the International Searching Authority.</p>	
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## 207 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include

the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

### *Summary of the Invention*

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

### *Detailed Description*

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig



analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard,  
5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained  
10 in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the  
15 filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages  
20 of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even  
25 lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include  
30 Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such  
35 as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

5       The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and  
10   double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability  
15   or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

      The polypeptide of the present invention can be composed of amino acids joined  
20   to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs,  
25   as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be  
30   branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a  
35   nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine,

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS -  
STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W.  
H. Freeman and Company, New York (1993); POSTTRANSLATIONAL  
COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic  
Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990);  
Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

## **Polynucleotides and Polypeptides of the Invention**

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

This gene is expressed primarily in melanocytes and, to a lesser extent, in testes, ovary, kidney and other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer, disorders of neural crest derived cells including pigmentation defects, melanoma, reproductive organ defects, and defects of the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin,

reproductive, and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating disorders that arise from alterations in the number or fate of neural crest derived cells including cancers such as melanoma and defects of the developing reproductive system.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 2**

This gene is expressed primarily in infant brain and fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental disorders of the brain or lung. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and pulmonary systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating or diagnosing disorders associated with abnormal proliferation of cells in the Central nervous system and developing lung.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 3**

This gene is expressed primarily in breast lymph node and to a lesser extent in ovarian cancer and chondrosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune responses such as inflammation or immune surveillance for

tumors. This gene may be important for inflammatory responses associated with tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 236 as residues: Lys-45 to Val-50, Lys-69 to Arg-76.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment or diagnosis of immune responses including those associated with tumor-induced inflammation.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 4**

This gene is expressed primarily in T-cells and T-cell lymphomas.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunological diseases involving T-cells such as inflammation, autoimmunity, and cancers including T-cell lymphomas. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of T-cells and other cells of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating T-cell based disorders such as inflammatory diseases, autoimmune disease and tumors including T-cell lymphomas.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 5**

This gene is expressed primarily in activated monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation, autoimmunity, infection, or disorders involving activation of monocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 238 as residues: Asp-19 to Arg-31.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing or treating diseases that result in activation of monocytes including infections, inflammatory responses or autoimmune diseases.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 6**

The translation product of this gene shares sequence homology with terminal deoxynucleotidyltransferase which is thought to be important in catalyzing the elongation of oligo- or polydeoxynucleotide chains.

This gene is expressed primarily in activated human neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly those of the blood such as leukemia and deficiencies in neutrophils such as neutropenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having

such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to terminal deoxynucleotidyltransferase indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and differential diagnosis of acute leukemia's. Alternatively, this gene may function in the proliferation of neutrophils and be useful as a treatment for neutropenia, for example, following neutropenia as a result of chemotherapy.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

The contig exhibits a reasonable homology to the human chorionic gonadotropic (HCG) analogue-GT beta-subunit as disclosed in U.S. Patent No. 5,508,261 and PCT Publication No. WO 92/22568. There is a high degree of conservation of the structurally important cysteine residues in these identities.

This gene is expressed primarily in IL-1 and LPS induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases of the immune system since expression is primarily in neutrophils, and may be useful as a growth factor for the differentiation or proliferation of neutrophils for the treatment of neutropenia following chemotherapy.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 8**

This gene is expressed primarily in IL-1- and LPS-induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 241 as residues: Ser-14 to Pro-22, Leu-43 to Val-53.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of diseases of the immune system since expression is primarily in neutrophils, and may be useful as a growth factor for the differentiation or proliferation of neutrophils for the treatment of neutropenia following chemotherapy.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 9**

This gene is expressed primarily in IL-1 and LPS induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the immune system, including inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 242 as residues: Tyr-22 to His-35.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases of the immune system since expression is primarily in neutrophils, and may be useful as a growth



factor for the differentiation or proliferation of neutrophils for the treatment of neutropenia following chemotherapy.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 10**

5        This gene is expressed primarily in activated T-cells and to a lesser extent in endothelial cells.

         Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are  
10       not limited to, immune dysfunctions including cancer of the T lymphocytes and autoimmune disorders and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at  
15       significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20       The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of immune disorders particularly of T-cell origin and may act as a growth factor for particular subsets of T-cells such as CD4 positive cells which would make this a useful therapeutic for the treatment of HIV and other immune compromising illnesses.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

         This gene is expressed primarily in fetal tissue.

         Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30       biological sample and for diagnosis of many developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected  
35       in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful as a growth factor or differentiation factor for particular cell types in the developing fetus and may be useful in replacement or other types of therapy in cases where the gene is expressed aberrantly.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 12**

10 This gene is expressed primarily in T-cells and to a lesser extent in tumor tissue including glioblastoma, meningioma, and Wilm's tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the immune system including autoimmune conditions such as  
15 rheumatoid arthritis, inflammatory disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
20 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 245 as residues:  
25 Thr-9 to Ser-14.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis/ modulation of immune function disorders, including rheumatoid arthritis and inflammatory responses.

#### **30 FEATURES OF PROTEIN ENCODED BY GENE NO: 13**

This gene is expressed primarily in placenta and to a lesser extent in fetal liver and bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
35 biological sample and for diagnosis of hematological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the hematological and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful as a growth factor for hematopoietic stem cells or progenitor cells in the treatment of chemotherapy patients or kidney disease.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 14**

This gene is expressed primarily in stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of hematopoietic disorders including cancer, neutropenia, anemia, and thrombocytopenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful as a growth factor for hematopoietic stem cells or progenitor cells, in particular following chemotherapy treatment.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 15**

The translation product of this gene shares sequence homology with epsilon-COP from *Bos taurus* which is thought to be important as a component of coatamer, a complex of seven proteins, that is the major component of the non-clathrin membrane coat. Preferred polypeptides encoded by this gene comprise the following amino acid sequences:

MAPPAPGPASGGSGEVDELFDVKNAFYIGSYQQCINEAXXVKLSSPERDVERD

VFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMFADYLAHESRRDSIVAELDRE  
 MSRSXDVTNTTFLDMAASTYLHDQNPDAALRALHQGDSLECTAMTVQILLKLD  
 RLDLARKELKRMQDLDEDATLTQLATAWVSLATGGEKLQDAYYIFQEMADKCS  
 PTTTTLLNGQAACHMAQGRWEAAEGLLQEALDKDSGYPETLVNLIVLSQHLGKP  
 5 PEVTNRYLSQLKDAHRSHPIKEYQAKENDFDRLVLQYAPSAEAGPELSGP  
 (SEQ ID NO:458); or RDVERDVFLYRAYLAQRKFGVVLDEIKPSSAPELQAVRMF  
 ADYLAHESRRDSIVAELDREMSRSXDVTNTTFLDMAASTYLHDQNPDAALRALH  
 QGDSLECTAMTVQILLKLDRLDLARKELKRMQDLDEDATLTQLATAWVSLATG  
 GEKLQDAYYIFQEMADKCSPTTTTTLLNGQAACHMAQGRWEAAEGLLQEALDKD  
 10 SGYPETLVNLIVLSQHLGKPPEVTNRYLSQLKDAHRSHPIKEYQAKENDFDRL  
 VLQYAPSA (SEQ ID NO:459).

This gene is expressed primarily in activated monocytes and T-cells, and to a lesser extent in multiple other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 15 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, immunomodulation, specifically relating to transport problems in these  
 cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
 providing immunological probes for differential identification of the tissue(s) or cell  
 20 type(s). For a number of disorders of the above tissues or cells, particularly of the  
 immune, expression of this gene at significantly higher or lower levels may be routinely  
 detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g.,  
 serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample  
 taken from an individual having such a disorder, relative to the standard gene  
 25 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 individual not having the disorder.

The tissue distribution and homology to epsilon-COP indicates that  
 polynucleotides and polypeptides corresponding to this gene are useful for treating  
 /diagnosing problems with the cellular transport of proteins that may result in  
 30 immunologic dysfunction.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 16

The translation product of this gene shares sequence homology with an RNA  
 helicase which is thought to be important in polynucleotide metabolism. The translation  
 35 product of this contig exhibits good homology to the LbeIF4A antigen of *Leishmania*  
*braziliensis*. The LbeIF4A antigen, or immunogenic portions of it, can be used to  
 induce protective immunity against leishmaniasis, specifically *L. donovani*, *L. chagasi*,

*L. infantum*, *L. major*, *L. braziliensis*, *L. panamensis*, *L. tropica* and *L. guyanensis*. It can also be used diagnostically to detect *Leishmania* infection or to stimulate a cellular and/or humoral immune response or to stimulate the production of interleukin-12.

This gene is expressed primarily in colon cancer and to a lesser extent in  
5 pituitary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of cancers particularly of the colon. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample  
15 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 249 as residues: Glu-93 to Ala-98, Gln-150 to Leu-156, Leu-220 to Leu-231, Leu-268 to Arg-273, Val-324 to Pro-341, Arg-372 to Asn-  
20 380, Ser-405 to Gly-410, Phe-426 to Ala-433, Glu-458 to Asp-470, Arg-506 to Ser-547.

The tissue distribution and homology to RNA helicase indicates that polynucleotides and polypeptides corresponding to this gene are useful for development of diagnostic tests for colon cancer.  
25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 17**

The translation product of this contig has sequence homology to a cytoplasmic protein that binds specifically to JNK designated the JNK interacting protein-1 or JIP-1 in mice. JIP-1 caused cytoplasmic retention of JNK and inhibition of JNK-regulated  
30 gene expression.

This gene is expressed primarily in brain including pituitary cerebellum frontal cortex, fetal brain and to a lesser extent in the kidney cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
35 biological sample and for diagnosis of the central nervous system disorders including ischemia, epilepsy, Parkinson's disease, and schizophrenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Furthermore, the translation product of this contig may suppress the effects of the JNK signaling pathway on cellular proliferation, including transformation by the Bcr-Abl oncogene. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 250 as residues: Pro-6 to Ser-26, Ala-30 to Asp-41, Gly-55 to Ser-61, Gly-74 to Thr-80, Tyr-117 to Ala-123, Tyr-167 to Asp-172, Ala-212 to Cys-223, Pro-239 to Tyr-244.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for enhanced survival and/or differentiation of neurons as a treatment for neurodegenerative disease.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 18

The translation product of this gene shares sequence homology with a liver stage antigen from a protozoan parasite.

This gene is expressed primarily in fetal tissue and to a lesser extent in activated T-cells and other immune cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental abnormalities and diseases of immune function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to a protozoan antigen indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/immune modulation of parasitic infections.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 19

Preferred polypeptide encoded by this gene comprise the following polypeptide sequences:

MKAIGIEPSLATYHHIIRLFDQPGDPLKRSSFIIYDIMNELMGKRFSPKD  
 PDDDKFFQSAMSICSSLRDLELAYQVHGLLKTGDNWKFIPDQHRNFYYSKFF  
 10 DLICLMEQIDVTLKWEYEDLIPSA YFPHSQTMHLLQALDVANRLEVIPKIWER  
 (SEQ ID NO:460); and/or KDSKEYGHTFRSDLREEILMLMARDKHPPQLQVAF  
 ADCAADIKSAYESQPIRQTAQDWPATSLNCIAILFLRAGRTQEA WKMLGLFRKH  
 NKIPRSELLNELMDSAKVSNPSQAIEVVELASAFSLPICEGLTQRVMSDFAINQ  
 EQKEALSNLTALTSDSDTDSSSDSDSDTSEGK (SEQ ID NO:461). Polynucleotides  
 15 encoding such polypeptides are also provided.

This gene is expressed primarily in stromal and CD34 depleted bone marrow cells and to a lesser extent in tissues of embryonic origin.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of hematologic origin including cancers and immune dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
 25 the hematopoietic and immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 30 fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 252 as residues: Ser-28 to Gln-34.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful as a growth factor for hematopoietic stem cells or progenitor cells which may be useful in the treatment of chemotherapy patients  
 35 suffering from neutropenia.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 20**

Preferred polypeptide fragments can be found in an alternative open reading frame. These preferred polypeptides comprise the amino acid sequence:

MSSDNESDIEDEDLKLELRRLRDKHLKEIQDLQSRQKHEIESLYTKLGKVPPAVI  
 5 IPPAAPLSGRRRRPTKSKGSKSSRSSSLGNKSPQLSGNLSGQSAASVLHPQQT  
 HPPGNIPESGQNQLLQPLKSPSSDNLYSFTSDGAISVPSLSAPGQGTSTNTV  
 GATVNSQAAQAQPPAMTSSRKGTFTDDLHKLVDNWARDAMNLSGRRGSKGH  
 MNYEGPGMARKFSAPGQLCISMTSNLGGSAISAASATSLGHFTKSMCPPQQY  
 GFPATPFGAQWSGTGGPAPQPLGQFQPVGTASLQNFNISNLQKSISNPPGSNL  
 10 RTT (SEQ ID NO:462); IQDLQSRQKHEIESLYTKLGKVPPAVIIPPAAPLSGRRRR  
 PTKSKGSKSSRSSSLGNKSPQLSGNLSGQSAASVLHPQQT  
 HPPGNIPESGQNQLLQPLKSPSSDNLYSFTSDGAISVPSLSAPGQGTST (SEQ ID NO:463);  
 TSDGAISVPSLSAPGQGTSTNTV  
 GATVNSQAAQAQPPAMTSSRKGTFTDDLH (SEQ ID NO:464); KGHMNYEGPGMARKFSAPGQLCISMTSNLGGSAISAAS  
 15 ATSLGHFTK (SEQ ID NO:465); QPLKSPSSDNLYSFTSDGAISVPSLSAPG  
 (SEQ ID NO:466). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed in fetal liver and tissues associated with the CNS.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, liver and CNS diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
 25 tissues or cells, particularly of the liver and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level  
 30 in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 253 as residues: Gln-26 to Lys-34.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment for liver diseases such  
 35 as hepatocellular carcinomas and diseases of the CNS.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 21**

In an alternative reading frame, this gene shows sequence homology to two recently cloned genes, karyopherin beta 3 and Ran\_GTP binding protein 5. (See Accession Nos. gi2102696 and gnllPIDle328731.) The Ran\_GTP binding protein is related to importin-beta, the key mediator of nuclear localization signal (NLS)-dependent nuclear transport. Based on homology, it is likely that this gene may activity similar to the RAN\_GTP binding protein. Preferred polypeptide fragments comprise the amino acid sequence: VRVAAAESMXLLLECAxVRGPEYLTQMWHFMCDALIKA IGTEPDSVDLSEIMHSFAK (SEQ ID NO:467). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed in thymus tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment for immune disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 22**

This gene is expressed primarily in prostate and osteoclastoma tissues. Preferred polypeptide fragments also comprise the amino acid sequence: MEINNQNCFIVIDLVRTVMENGVEGLLIFGAFLPESWLVRCSSPEPKALLLIL AHSQKRRLDGWSFIRHLRVHYCVSLTIHFS (SEQ ID NO:468). Also preferred are polynucleotide sequences encoding this polypeptide fragment.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, bone and prostate diseases, and cancers, particularly of the bone and prostate. Similarly, polypeptides and antibodies directed to these polypeptides are

useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone and prostate systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
5 tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 255 as residues: Met-1 to Ser-11.

10 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment for bone and prostate disorders, especially cancers of those systems.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 23**

15 This gene shares sequence homology with the FK506-binding protein (FKBP-13) family, a known cytosolic receptor for the immunosuppressants. Recently, another group has cloned a very similar gene, recognizing the homology to FK506-binding protein family, calling their gene FKBP23. (See Accession No. 2827255.)

This gene is expressed primarily in lymphoid tissues.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample, especially for those susceptible to immune suppressant therapies and for diagnosis of diseases and conditions, which include, but are not limited to, immune suppressant disorders. Similarly, polypeptides and antibodies directed to these  
25 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or  
30 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 256 as residues: Ala-19 to Val-31, Arg-38 to Gly-49, Ala-61 to Lys-66, Tyr-68 to Pro-78, Gly-116 to Ala-121, Asp-154 to  
35 Ser-162, Glu-173 to Gln-186, Phe-194 to Gly-203, Pro-207 to Val-212.

The tissue distribution and homology to FKBP-12 and -13 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment for immune suppressant disorders.

#### 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 24

This gene is expressed primarily in the brain and in the retina. This gene maps to chromosome 8, and therefore can be used in linkage analysis as a marker for chromosome 8.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological and ocular associated disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological  
15 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or  
20 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 257 as residues: Cys-34 to Asp-40.

The tissue distribution in retina indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of eye disorders  
25 including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma. Expression in the brain indicates a role in the is useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive  
30 disorder and panic disorder.

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#### FEATURES OF PROTEIN ENCODED BY GENE NO: 25

This gene shows sequence homology to a newly identified class of proteins expressed in the nervous system, called stathmin family. (See Accession No. 2585991;  
35 see also Eur. J. Biochem. 248 (3), 794-806 (1997).) The stathmin family appears to be an ubiquitous phosphoprotein involved as a relay integrating various intracellular signaling pathways. These pathways affect cell proliferation and differentiation.

Preferred polypeptide fragments comprise the amino acid sequence:

QDKHAEVVRKNKELKEEASR (SEQ ID NO:469); QQDLSPWAAPVGCPLXXASX  
TCHXLPLSGCLRRQXSXSLPVVAXLCFWFSCPLASLFVPGQPCVTCPPFSLPFQD  
KHAEVVRKNKELKEEASR (SEQ ID NO:470). Also preferred are the

5 polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
10 not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to  
these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the central nervous system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
15 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
such a disorder, relative to the standard gene expression level, i.e., the expression level  
in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
20 corresponding to this gene are useful for the detection/treatment of neurodegenerative  
disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's  
Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive  
compulsive disorder and panic disorder.

## 25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 26**

The polynucleotide sequence of this gene contains a domain similar to a Flt3  
ligand peptide. Preferred polypeptide fragments comprise the amino acid sequence:  
PTRCCTTQPCRSSARRPCWVPMVPSPEGREXQPTCPS (SEQ ID NO:471). Thus,  
this gene may have activity as binding to Flt3 receptors, a process known to promote  
30 angiogenesis and/or lymphangiogenesis.

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This gene is expressed in human tonsil, and to a lesser extent in  
teratocarcinoma, placenta, colon carcinoma, and fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for identification of the tissue(s) or cell type(s) present in a biological sample  
35 and for diagnosis of diseases and conditions, which include, but are not limited to,  
diseases of the tonsil, as well as cancers, such as colon, reproductive, and kidney  
cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful

in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tonsils, colon, reproductive organs, and kidneys, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 259 as residues: Pro-22 to Glu-33.

The tissue distribution in tonsil and several cancers and fetal tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the tonsil or colon, such as tonsillitis, inflammatory diseases involving nose and paranasal sinuses, especially during the infection of influenza, adenoviruses, parainfluenza, rhinoviruses. The gene may also be useful in the diagnosis and treatment of neoplasms of nasopharynx or colon origins.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In an alternative reading frame exists a large open reading frame that encodes a preferred polypeptide. Preferred polypeptide fragments comprise the amino acid sequence:

MKRSLNENSARSTAGCLPVPLFNQKKRNRQPLTSNPLKDDSGISTPSDNYDFP  
 PLPTDWAWEAVNPEXAPVMKTVDTGQIPHVSVRPLRSQDSVFNSIQSNTGRSQ  
 GGWSYRDGNKNTSLKTDWXXKNDKFKPQCKRTNLVANDGKNSCPMSSGAQQQK  
 QLRTPPEPPNLSRNKETELLRQTHSSKISGCTMRGLDKNSALQTLKPNFQQNQY  
 KXQMLDDIPEDNTLKETSLYQLQFKEKASSLRISA VIESMKYWREHAQKT VLL  
 FEVLAVLDSAVTPGPYYSKTFLMRDGNKNTLPCVFYEIDREL PRLIRGRVHRCVG  
 NYDQKKNIFQCVSVRPASVSEQTFQAFVKIADVEMQYYINVMNET (SEQ ID  
 NO:472); SQDSVFNSIQSNTGRSQGGWSYRDGNKNTSLKTDWXXKNDKFKPQCKR  
 (SEQ ID NO:473); NKETELLRQTHSSKISGCTMRGLDKNSALQTLKPNF (SEQ ID  
 NO:474); SSLRISA VIESMKYWREHAQKT VLLFEVLAVLDSAVTPGPYYSKTFLM  
 (SEQ ID NO:475); and PRLIRGRVHRCVGNYDQKKNIFQCVSVRPASVSEQTF  
 QAFV (SEQ ID NO:476).

This gene is expressed primarily in human testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, male reproductive disorders, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful as a hormone with reproductive or other systemic functions; contraceptive development; male infertility of testicular causes, such as Klinefelter's syndrome, varicocele, orchitis; male sexual dysfunctions; testicular neoplasms; and inflammatory disorders such as epididymitis.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 28**

This gene is expressed primarily in apoptotic T-cell.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases relating to T cells, as well as cancer in general. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the disorders of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for immune disorders. Moreover, since the gene was isolated from an apoptotic cell and based on the understanding of the relationship of apoptosis and cancer, it is likely that this gene may play a role in the genesis of cancer.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 29**

This gene is expressed primarily in human tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, gastrointestinal disorders. Similarly, polypeptides and antibodies directed  
 to these polypeptides are useful in providing immunological probes for differential  
 10 identification of the tissue(s) or cell type(s). For a number of disorders of the above  
 tissues or cells, particularly of the gastrointestinal system, expression of this gene at  
 significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
 fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
 15 such a disorder, relative to the standard gene expression level, i.e., the expression level  
 in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
 corresponding to this gene are useful for the diagnosis and treatment of gastrointestinal  
 diseases.

**20 FEATURES OF PROTEIN ENCODED BY GENE NO: 30**

The translation product of this gene shares sequence homology with C44C1.2  
 gene product of *Caenorhabditis elegans* with unknown function. Preferred polypeptide  
 fragments comprise the amino acid sequence:

GVFRPCVCGRPASLTCSPLDPEVGPYCDTPTMRTLFNLLWLALACSPVHTTLSK  
 25 SDAKKAASKTLLEKSQFSDKPQDRGLVVTDLKAESVVLEHRSYCSAKARDRH  
 FAGDVLGYVTPWNSHGYDVTKVFGSKFTQISPVWLQLKRRGREMFVETGLHD  
 VDQGWMRAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDEIEELSKTVVQVA  
 KNQHFDGFVVEVWNQLLSQKRVGLIHMLTHLAEALHQAARLLALLVIPPAITPGT  
 DQLGMFTHKEFEQLAPVLDGFSMLTYDYSTAHPGPNAPLSWVRACVQVLDP  
 30 KXKWRTKSSWGSTSMXWTXRPXDARXPVVGXRQIXLKDHXPRMVLDISK  
 PQ (SEQ ID NO:477); TCSPLDPEVGPYCDTPTMRTLFNLLWLALACSPVHTTLS  
 (SEQ ID NO:478); LVVTDLKAESVVLEHRSYCSAKARDRHFAAGDVLGYVTPW  
 NSHGYDVTKVFGSKF (SEQ ID NO:479); REMFEVETGLHDVDQGWMRAVRK  
 HAKGLHIVPRLLFEDWTYDDFRNVLDSEDE (SEQ ID NO:480); HFDGFVVEVW  
 35 NQLLSQKRVGLIHMLTHLAEALHQAARLLALLVIPPAITPGTDQLGM (SEQ ID  
 NO:481); DGFSLMTYDYSTAHPGPNAPLSWVRACVQVLDPKXKWRTKSSW  
 GST (SEQ ID NO:482). Also preferred are polynucleotide fragments encoding these

polypeptide fragments. This gene maps to human chromosome 11, and therefore is useful in linkage analysis as a marker for chromosome 11.

This gene is expressed primarily in human T cells and to a lesser extent in human colon carcinoma.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
10 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from  
15 an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 263 as residues: Leu-21 to Ala-30, Ser-38 to Asp-47, Pro-87 to Asp-94, Leu-197 to Thr-204, Pro-256 to Ser-262, Thr-277 to Arg-282, Thr-293 to Trp-303.

20 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders and gastrointestinal diseases.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 31**

25 The translation product of this gene shares sequence homology with Ribosomal protein L11 of *Caenorhabditis elegans*. (See Accession No. 156201.) Preferred polypeptide fragments comprise the amino acid sequence:  
ERGVSINQFCKEFNERTKDIKEGIPLPTKILVKPDRTFEIKIGQPTVSYFLKAAAG  
IEKGARQTGKEVAGLVTLKHVYEIARIKAQDEAFALQDVPLSSVVRSIIGSARSL  
30 GIRVVKDLSSEELAAF QKERAIFLAAQKEADLAAQEAAKK (SEQ ID NO:483).  
Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed in human embryo tissue and to a lesser extent in human epithelioid sarcoma and other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as  
35 reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, development disorders and epithelial cell cancer. Similarly, polypeptides and antibodies



directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the embryonic and epithelial cell systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 264 as residues: Lys-34 to Gly-40.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of developmental disorders and epithelial cancer.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 32**

This gene is expressed primarily in resting T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammatory and general immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders of immune system.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 33**

This gene is believed to reside on chromosome 1. Accordingly, polynucleotides derived from this gene are useful in linkage analysis as chromosome 1 markers.

This gene is expressed primarily in prostate and to a lesser extent in soares adult brain, human umbilical vein endothelial cells, and amniotic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, prostate-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary system and nervous system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for the diagnosis and treatment of disorders of the urinary and nervous systems.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene shares sequence homology with R05G6.4 gene product. (See Accession No. gil1326338.) This gene also shares sequence homology with the cyclophilin-like protein CyP-60. (See Accession No. 1199598, see also Biochem. J. 314 (1), 313-319 (1996).) Preferred polypeptide fragments comprise the amino acid sequence:  
 AVYTYHEKKKDTAASGYGTQNIRLSRDAVKDFDCCCLSLQPCHDPVVTPDGYL  
 YERE AILEYILHQKKEIARQMKA YEKQRGTRREEQKELQRAASQDHVRGFLEKE  
 SAIVSRP LNPFTAKALSGTSPDDVQPGPSVGPPSKDKDKVLPFSWIPSLTPEAK  
 ATKLEKPSRTVTCMSGKPLRMSDLTPVHFTPLDSSVDRVGLITRSEYVCAVT  
 RDSLSNATPCA VLRPSGAVVTLECEVEKLIRKDMVDPVTGDKLTDRDIIVLQRG  
 T (SEQ ID NO:484); YLYERE AILEYILHQKKEIARQMKA YEKQRGTRREEQKELQ  
 RAASQDHVRGFLE (SEQ ID NO:485); and FTA KALSGTSPDDVQPGPSVGPP  
 SKDKDKVLPFSWIPSLTPEAKATKLEKPSRTVTCMSGKPL (SEQ ID NO:486).  
 Also preferred are polynucleotide fragments that encode these polypeptide fragments.

This gene is expressed primarily in human testis and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, male reproductive disorders and in particular testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system. Expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders of the male reproductive system and in particular of testicular cancer.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 35**

The translation product of this gene shares sequence homology with Lpe5p of *Saccharomyces cerevisiae* which is thought to be important in the metabolism of phospholipids.

This gene is expressed primarily in liver and brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic and nervous systems expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 268 as residues: Pro-14 to Leu-20, Lys-28 to Asn-38, Arg-109 to Arg-114, Lys-119 to Asn-124, Glu-152 to Leu-157, Pro-172 to Val-180.

The tissue distribution and homology to Lpe5p of *Saccharomyces cerevisiae* indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of metabolic and nervous disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 36**

This gene shares sequence homology with the nuclear ribonucleoprotein U (HNRNP U), encoded by *C. elegans* (See Accession gil1703576.) Preferred polypeptide fragments comprise the amino acid sequence:

- 5 MDTSENRPENDVPEPPMPIADQVSNDDRPEGSVEDEEKKESSLPKSFKRKISVV  
SATKGVPAAGNSDTEGGQPGRKRRWGASTATTQKKPSISITTESLKS LIPDIKPL  
AGQEAVVDLHADDSETERNGDDGTHDKGLKICRTVTQVVP AEGQENGQ  
REEEEEKEPEAEPPVPPQVSVEVALPPPAEHEVKKVTLGDTLTRRSISQQKSGV  
SITIDDPVRTAQVPSPPRGKISNIVHISNLVRPFTLGQLKELLGRTGTLVEEAFWI  
10 DKIKSHCFVTYSTVEEAVATRTALHG VKWPQSNPKFLCADYAEQDELDYHRGL  
LVDRPSETKTEEQGI PRPLHPPPPPPVQPPQHPRAEQREQERAVREQWAERERE  
MERRERTRSEREWRDKVREGPRSRSRSRXRRRKERAKSKEKKSEKKEKAQE  
EPPAKLLDDLFRKTKAAPCIYWLPLTDSQIVQKEAERAERAKEREKRRKEQEEE  
EQKEREKEAERERNRQLEREKRREHSRERDRERERERERDRGDRDRDRERDRE  
15 RGRERDRRDTKRHSR SRSTPVRDRGGR (SEQ ID NO:488). Also preferred are  
the polynucleotide fragments encoding this polypeptide fragments.

This gene is expressed primarily in epididymus.

- Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
20 biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, diseases of the male reproductive system. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the male reproductive system, expression of  
25 this gene at significantly higher or lower levels may be routinely detected in certain  
tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,  
urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
30 disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
corresponding to this gene are useful for the diagnosis and treatment of male  
reproductive disorders.

**35 FEATURES OF PROTEIN ENCODED BY GENE NO: 37**

This gene is expressed primarily in amygdala.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammatory diseases and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the amygdala, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory diseases and reproductive disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 38**

This gene shares sequence homology with human opsonin protein P35 fragment. (See Accession No. R94181.) The opsonin protein activates the phagocytosis of pathogenic microbes by phagocytic cells. Preferred polypeptide fragments comprise the amino acid sequence: GCDSCPHLPREAFAQDTQAECESSRAERADMCPDAP PSQEVPEGPGAAP (SEQ ID NO:489). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed in immune-related tissues such as thymus, macrophage, T cells and to a lesser extent in many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders and infectious disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and infectious disease, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 271 as residues: Lys-9 to Arg-14, Met-38 to Asp-51.

- 5 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders, as well as the treatment and/or diagnosis of infectious disease.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 39**

- 10 The translation product of this gene shares sequence homology with alpha-2 type I collagen which is thought to be important in tissue repair. (See, e.g., 211607.) Preferred polypeptide fragments comprise the amino acid sequence: PQLPSCGRPWP  
PGTASVFQSHQTQGPREDPDPCRAQGSAGTHCPISLSPPRQ (SEQ ID NO:490). Also preferred are the polynucleotide sequences encoding these polypeptide sequences.

- 15 This gene is expressed primarily in the brain and to a lesser extent in the kidney and thymus

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, brain, kidney, and immune disorders. Similarly, polypeptides and  
20 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, kidney, and immune disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum,  
25 plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 30 The tissue distribution and homology to alpha-2 type I collagen indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of tissue repair, and brain, kidney, immune disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 40**

- 35 The translation product of this gene shares sequence homology with mini-collagen which is thought to be important in tissue repair tumor metastasis. (See Accession No. gnlIPID1006976.) Preferred polypeptide fragments comprise the amino acid sequence: PGFRGPSGLGCSFFPRSLGRVLPPGCQRPGAHAD

SSPPPTP (SEQ ID NO:491). Also preferred are polynucleotides encoding this polypeptide fragment.

This gene is expressed in ovarian cancer and to a lesser extent in dendritic cells and smooth muscle.

- 5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, tumor metastasis and tissue repair. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes
- 10 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor metastasis and tissue repair, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from
- 15 an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 273 as residues: Asn-2 to His-11.

- The tissue distribution and homology to mini-collagen gene indicates that
- 20 polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of tumor metastasis and tissue repair.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

- This gene shares sequence homology with the HIV TAT protein. (See
- 25 Accession No. 328416.) Preferred polypeptide fragments comprise the amino acid sequence: EDLKKPD PASLRAASCGEGKKRKACKNCTCGLAE ELEKEK SREQMSSQPKSACGNCYLGD AFRASC PYLGMPAFKPG EKVLLS (SEQ ID NO:492); EDLKKPD PASLRAASCGEGKKRKACKNCTCGLAE ELEKEK SREQMSSQPKSACGNCYLGD AFRASC PYLGMPAFKPG EKVLLS SDSNLHD
- 30 (SEQ ID NO:493); CGNCYLGD AFRASC PYLGMPAFKPG EKVLLS SDS (SEQ ID NO:494); SCGEGKKRKACKNCTCGLAE ELEKE (SEQ ID NO:495); SQPKSAC GNCYLGD AFRASC (SEQ ID NO:496); and REAGQNSERQYVS LSRD (SEQ ID NO:497). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

- 35 This gene is expressed primarily in the infant brain and to a lesser extent in the breast and testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, brain, testes and breast disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, testes and breast disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 274 as residues: Pro-7 to Val-15.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of brain, testes and breast, and other related disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 42**

This gene is expressed primarily in the infant brain, human cerebellum, and to a lesser extent in medulloblastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, brain related disorders and medulloblastoma and other brain cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain related disorders and brain cancers, including medulloblastoma, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 275 as residues: Thr-41 to Glu-47.



The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of human brain related disorders, brain cancers, and medulloblastoma.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 43

The translation product of this gene shares sequence homology with a phosphotyrosine-independent ligand for the lck SH2 domain which is thought to be important in signal transduction related to phosphotyrosine-independent ligand for the lck SH2 domain. (See Accession No. gi1184951.) Preferred polypeptide fragments  
 10 comprise the amino acid sequence: ESSGQARTLADPGPGWPRQQGMCFGSLT  
 GLSTTPHGFLTVSAEADPRLIESLSQMLSMGFSDEGGWLTRLLQTKNYDIGAAL  
 DTIQYSKH (SEQ ID NO:498). Also preferred are polynucleotide fragments encoding this polypeptide fragment. It is likely that this gene is a new member of a family of phosphotyrosine-independent ligands for the lck SH2 domains.

15 This gene is expressed primarily in the placenta and to a lesser extent in endothelial cells and neutrophil.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are  
 20 not limited to, reproductive, cardiovascular, immune, and infectious diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular, reproductive, and immune system, and infectious diseases, expression  
 25 of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the  
 30 disorder.

The tissue distribution and homology to a phosphotyrosine-independent ligand for the lck SH2 domain indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cardiovascular, reproductive, and immune system diseases, as well as infectious diseases.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

This gene is expressed primarily in the fetal brain, cerebellum and to a lesser extent in the placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neuronal cell related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal cell related disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 277 as residues: Thr-20 to Gly-28.

The tissue distribution and homology to proline-rich protein genes indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuronal cell related disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 45**

The translation product of this gene shares sequence homology with precerebellin of human, which is thought to be important in synaptic physiology. (See Accession No. gil180251.) It has been observed that cerebellin-like immunoreactivity is associated with Purkinje cell postsynaptic structures. Thus, it is likely that this gene also have synaptic activity. Preferred polypeptide fragments comprise the amino acid sequence: QEGSEPVLLEGECLVCEPGRAAAGGPGGAALGEAPPGRVAFXAV RSHHHEPAGETGNGTSGAIYFDQVLVNEG GGFDRASGSFVAPVRGVYSFRFH VVKVYNRQTVQVSLMLNTWPVISAFANDPDVTREAATSSVLLPLDPGDRVSLR LRRGXSTGW (SEQ ID NO:499). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in cerebellum and infant brain. By Northern analysis, a single transcript of 2.4 kb was observed in brain tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, neuronal cell signal transduction and synaptic physiology. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal cell signal transduction and synaptic physiology expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to gene or gene family indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuronal cell related disorders.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 46**

This gene is expressed in fetal liver and spleen, and to a lesser extent in bone marrow, umbilical vein, and T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders of the immune system, particularly hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoiesis and immune disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 279 as residues: Asp-30 to Glu-57.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of hematopoietic and immune disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 47**

The translation product of this gene shares sequence homology with a 12 kD nucleic acid binding protein of Feline calicivirus which is thought to be important in viral replication. (See Accession No. 59264)

5 This gene is expressed primarily in human cardiomyopathy and to a lesser extent in T helper cells, fetal brain and synovial sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cardiomyopathy as well as viral infection. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 280 as residues: Trp-20 to Cys-26.

The tissue distribution in cardiomyopathy and homology to viral 12 kD nucleic acid binding protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of cardiomyopathy, including those caused by ischemic, hypertensive, congenital, valvular, or pericardial abnormalities.

25 The gene expression pattern may be the consequence or the cause for these conditions.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 48**

The translation product of this gene shares sequence homology with tumor necrosis factor related gene product which is thought to be important in tumor necrosis, bacterial and viral infection, immune diseases and immunoreactions.

This gene is expressed primarily in colon and to a lesser extent in ovarian and breast cancers.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, tumors of colon, ovary or breast origins. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes

for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the colon, ovary and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to Tumor necrosis factors indicates that polynucleotides and polypeptides corresponding to this gene are useful for intervention of cancers of colon, ovary and breast origins, because TNF family members are known to be involved in the tumor development.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 49

The translation product of this gene shares sequence homology with mucins, such as epithelial mucin, which is thought to be important in extracellular matrix functions such as protection, lubrication and cell adhesion (See for example Accession No. R68002). Preferred polypeptide fragments comprise the following amino acid sequence: PRSRPALRPGRQRPPSHSATSGVLRPRKKPDP (SEQ ID NO:500).

Also preferred are polynucleotide fragments encoding these polypeptide fragments. Moreover, this gene maps to chromosome 22q11.2-qter, and therefore, can be used as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in corpus colosum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, tumors, especially of corpus colosum, as well as metastatic lesions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the corpus colosum and other solid tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to mucins indicates that polynucleotides and polypeptides corresponding to this gene are useful for serum tumor markers or immunotherapy targets because tumor cells have greatly elevated level of mucin expression and shed the molecules into the epithelial tissues.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 50**

This gene is expressed primarily in CD34 depleted buffy coat cord blood and primary dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematopoietic disorders and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For  
15 a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard  
20 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34 depleted buffy coat cord blood and primary dendritic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of hematopoietic and immune disorders.  
25 Secreted or cell surface proteins in the above tissue distribution often are involved in cell activation (e.g. cytokines) or molecules involved in cell surface activation.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 51**

The translation product of this gene shares sequence homology with Interferon  
30 induced 1-8 gene encoded polypeptide which is thought to be important in binding to retroviral rev responsive element. Preferred polypeptide fragment comprise the following amino acid sequences: MTLITPSXKLTFXKGNKSWSSRACSSSTLVDP (SEQ ID NO:501). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

35 This gene is expressed primarily in CD34 positive cells and neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, retroviral infection, such as AIDS, and other immune disorders.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 284 as residues: Gln-51 to Trp-62.

The tissue distribution and homology to interferon induced gene 1-8 indicates that polynucleotides and polypeptides corresponding to this gene are useful for intervention of retroviral infection including HIV. The factor may be involved in viral stability or viral entry into the cells. Alternatively, the virus/factor complex may elicit the cellular immune reaction.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 52**

This gene shares sequence homology to immunoglobulin lambda chain (See Accession No. 2865484). Therefore it is likely that this gene has activity similar to an immunoglobulin lambda chain. Preferred polypeptide fragments comprise the following amino acid sequence: GHPSPALSIAPSDGSQLPCDEVGYGEAHVTRYCKKPLTNS HLETEAQSSSL (SEQ ID NO:502). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in Hodgkin's lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, Hodgkin's lymphoma and other immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 285 as residues: Pro-27 to Thr-32.

5 The tissue distribution in Hodgkin's lymphoma and the sequence homology indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis of Hodgkin's lymphoma, since the elevated expression and secretion by the tumor mass may be indicative of tumors of this type. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune  
10 functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 53**

This gene has extensive homology to cDNA for Homo sapiens mRNA for the  
15 ISLR gene(See Accession No. AB003184). This protein is considered to be a new member of the Ig superfamily and contains a leucine-rich repeat (LRR) with conserved flanking sequences and a C2-type immunoglobulin (Ig)-like domain. These domains are important for protein-protein interaction or cell adhesion, and therefore it is possible that the novel protein ISLR may also interact with other proteins or cells. The ISLR gene  
20 was mapped on human chromosome 15q23-q24 by fluorescence in situ hybridization (See Medline Article No. 97468140). Homology to the ISLR gene has been confirmed by another independent group as well (See Accession No. Hs.102171)

This gene is expressed in a number of tissues including human retina, heart, skeletal muscle, prostate, ovary, small intestine, thyroid, adrenal cortex, testis,  
25 stomach, spinal cord, fetal lung and fetal kidney tissues, colon, tonsil and stomach cancer, and to a lesser extent in endometrial stromal cells treated with estradiol, breast tissue, synovium, lymphoma, and number of other tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, tumors of colon, ovary and breast origins. However, due to the wide range of expression in various tissues, protein may play a vital role in the development of cancer in other tissues as well, not just those mentioned above. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
35 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the colon, ovary and breast, expression of this gene at significantly higher or lower levels may be routinely



detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Additionally, this gene maps to chromosome 15q23-q24, and therefore, can be used as a marker in linkage analysis for chromosome 15.

The tissue distribution in tumors of colon, ovary, and breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 54

Gene has homology to multidrug resistance gene 1 (See Accession No. P06795). Preferred polynucleotide fragments comprise the following sequence:  
 GCTTCGTGTCCAACCCTCTTGCCCTTCGCCTGTGTGCCTGGAGCCAGTCCCA  
 CCACGCTCGCGTTTCCTCCTGTAGTGCTCACAGGTCCCAGCACCGATGGCA  
 TTCCCTTTGCCCTGAGTCTGCAGCGGGTCCCTTTTGTGCTTCCTTCCCCTCA  
 GGTAGCCTCTCTCCCCCTGGGCCACTCCCGGGGGTGAGGGGGTTACCCCTT  
 CCCAGTGTTTTTTATTCCTGTGGGGCTACCCCAAAGTATTAAGTAGCTTT  
 GTAA (SEQ ID NO:503). Also preferred are polypeptide fragments encoded by these polynucleotide fragments.

This gene is expressed primarily in lung, esophagus, leukemia (Jurkat cells) and breast cancers and to a lesser extent in macrophages treated with GM-CSF fetal tissues and wide range of tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer of wide range of origins. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the solid tumors, lung and leukemia, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Furthermore, due to the high expression level in lung tissue and the proposed function of the multidrug resistance protein 1 gene as the efflux pump responsible for low-drug accumulation in multidrug-resistant cells, protein as well mutants thereof, may also be beneficial as a target for gene therapy, particularly for the chronic patient. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 287 as residues: Met-1 to Lys-16.

The tissue distribution in wide range of cancers and fetal tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection of cells in active proliferation, such as cancers. The gene products may be used for cancer markers or immunotherapy target.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 55**

This gene maps to the X chromosome.

This gene is expressed primarily in the brain and to a lesser extent in the developing embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurodegenerative disease states and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders, including sex-linked disorders, of the above tissues or cells, particularly of the neurological, developmental systems, and cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Moreover, this gene maps to the X chromosome, and therefore, may be used as a marker in linkage analysis for this chromosome.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Klinefelter's, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental

disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 56

- 5 The translation product of this gene shares sequence homology with paxillin which is thought to be important in mediating signal transduction from growth factor receptors to the cytoskeleton. Preferred polynucleotide fragments comprise the following sequence: TGGCTCACTGTCTTACAATCACTGCTGTGGAATCATGA TACCACITTTAGCTCTTTGCATCTTCCTTCAGTGTATTTTGTITTTTCAAGAGG
- 10 AAGTAGATTTTAACTGGACAACITTTGAGTACTGACATCATTGATAAATAAACT GGCTTGTGGTTTCAA (SEQ ID NO:506). Also preferred are polypeptide fragments encoded by these polynucleotide fragments. More preferably, polypeptide fragments comprise the amino acid sequence: LDELMAHLTEMQAKVAVRAD
- 15 AGKKHLPDKQDHKASLD SMLGGLEQELQDLGIATVPKGHCASCQKPIAGKVI HALGQSWHPEHFVCTHCKEEIGSSPFFERSGLXYCPNDYHQLFSPRCAYCAAP ILDKVLTAMNQTWHPEHFFCSHCGEVFGAEGFHEKDKKPYCRKDFLAMFSPK CGGCNRPVLENYLSAMDTVWHPECFVCGDCFTSFSTGSFFELDGRPFCELHYH HRRGTLCHGCGQPITGR CISAMGYKFHPEHFVCAFCLTQLSKGIFREQNDKTY CQPCFNKLF (SEQ ID NO:507); KASLD SMLGGLEQELQDLGIATVPKGHC
- 20 ASCQKPIAGKVIHAL (SEQ ID NO:508); CPNDYHQLFSPRCAYCAAPILDKVL TAMNQTWHPEHFFCSHCGEVFGAEG (SEQ ID NO:509); DKKPYCRKDFLAM FSPKCGGCNRPVLENYLSAMDTVWHPECFVCGDCFTSFSTGSFFELDGRPFCE L (SEQ ID NO:510); CGQPITGR CISAMGYKFHPEHFVCAFCLTQLSKGIFRE QNDKTYCQ (SEQ ID NO:511). Polynucleotide fragments encoding these preferred
- 25 polypeptide fragments are also contemplated.

This gene is expressed primarily in brain, and to a lesser extent in the developing embryo.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
- 30 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological disease states and developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and
- 35 nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or

cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Moreover, since this gene shares homology with a gene that maps to chromosome 11, (See Accession No.T87404), gene as well as its translated product may be used for linkage analysis on chromosome 11.

The tissue distribution and homology to paxillin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and or detection of disease states associated with abnormal signal transduction in brain and/or the developing embryo. This would include treatment or detection of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder and also in the treatment and or detection of embryonic development defects.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

This gene is expressed primarily in fetal spleen, brain, and to a lesser extent in six week old embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders, neurological disorders, and developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 290 as residues: Arg-28 to Gly-34.

The expression of this gene in fetal spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/detection of immune disorders such as arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. In addition the expression of this gene in the early embryo, indicates a key role in embryo development and hence the gene or gene product could be used in the treatment and or detection of embryonic development defects. This would include

treatment or detection of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntintons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder and also in the treatment and or detection of embryonic development defects.

5

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 58

The translation product of this gene shares sequence homology with the gene disrupted in the neurodegenerative disease dentatorubal-pallidoluyasian atrophy. Moreover a long open reading fame exists in an alternative frame. Preferred polypeptide fragments

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comprise the following:

MGSSQSVEIPGGGTEGYHVLRVQENSPGHRAGLEPFFDFIVSINGSRLNKDND  
 TLKDLLKXNVEKPKMLIYSSKTLELRETSVTPSNLWGGQGLLGVSIRFCSFD  
 GANENVVHVLVESNSPAALAGLRPHSDYIIGADTMNESEDLSLIETHEAKP  
 LKLYVYNTDTDNCREVIITPNSAWGGEGSLGCGIGYGYLHRIPTRPFEEGKKIS  
 15 LPGQMAGTPITPLKDGFTVQLSSVNPPSLSPPGTTGIEQSLTGLSISSTPPAVSS  
 VLSTGVPTVPLLPPQVNQSLTSVPPMNPATTLPGLMPLPAGLPNLPNLPNLP  
 PHIMPGVGLPELVNPGLPPLPSMPPRNLPGLPPLPSEFLPSFPLVPESSAASS  
 GELLSSLPPTSNAPSDPATTTAKADAASSLTVDVTPPTAKAPTTVEDRVGDSTPV  
 SEKPVSAAVDANASESP (SEQ ID NO:512); SVEIPGGGTEGYHVLRVQENSPGH  
 20 RAGLEPFFDFIVSINGSRLNKDNDTLKDLLKXNVEKPKMLIYSSKTLELRETS  
 VTPSNLWGGQGLLGVSIRFCSFDGANENVVH (SEQ ID NO:513); ESNSPA  
 LAGLRPHSDYIIGADTMNESEDLSLIETHEAKPLKLYVYNTDTDNCREVIITP  
 NSAWGGEGSLGCGIGYGYLHRIPTRPFEEGKKISLPGQMAGTPITPLKDGFTV  
 QLSSVNPPSLSPPGTTGIEQSLTG LSISS (SEQ ID NO:514); RIPTRPFEEGKKI  
 25 SLPGQMAGTPITPLKDGFTVQLSSVNPPSLSPPGTTGIEQSLTGLSISSTPPAVS  
 SVLSTGVPTVPLLPPQVNQSLTSVPPMNPATTLPGLMPLPAGLPNLPNLPNLP  
 APHIMPGVGLPELVNPGLPPLPSMPPRN (SEQ ID NO:516); PGLPPLPSMPPRN  
 LPGIAPLPSEFLPSFPLVPESSAASSGELLSSLPPTSNAPSDPATTTAKADAA  
 SSLTVDVTPPTAKAPTTVEDRVGDSTPVSEKPVSAAVDAN (SEQ ID NO:517).

30

This gene is expressed primarily in prostate cancer, and to a lesser extent in the pineal glands and in fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological conditions and pulmonary disorders. Similarly,

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polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For

a number of disorders of the above tissues or cells, particularly of the nervous, pulmonary, and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 291 as residues: Asn-9 to Leu-14.

The abundance of this gene in the pineal gland and its homology to a gene disrupted in the neurodegenerative disease state Dentatorubral-pallidoluysian atrophy indicates that this gene may be useful in the treatment and/or detection of other neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. The abundance of this gene in fetal lung would suggest that misregulation of the expression of this protein product in the adult could lead to lymphoma or sarcoma formation, particularly in the lung; that it may also be involved in predisposition to certain pulmonary defects such as pulmonary edema and embolism, bronchitis and cystic fibrosis; and thus the gene or the gene protein encoded by the gene could be used in the detection and/or treatment of these pulmonary disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 59**

This gene is expressed primarily in the developing embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The expression of this gene primarily in the embryo, indicates the gene plays a key role in embryo development and that the gene or the protein encoded by the gene could be used in the treatment and or detection of developmental defects in the embryo or in infants.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 60**

This gene displays homology to nestin, an intermediate filament protein, the expression of which correlates with the proliferation of Central Nervous System progenitor cells and that is useful in the identification of brain tumors. This gene maps  
10 to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1 (See Accession No. AA527348).

This gene is expressed primarily in kidney and to a lesser extent in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
15 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, renal disorders and neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the excretory and  
20 nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
25 individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 293 as residues: Thr-128 to Asn-135.

The tissue distribution and homology to nestin indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection and/or treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease,  
30 Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, its abundance in kidney indicates that it is useful in the treatment and detection of acute renal failure and other disease states associated with the kidney.

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#### **35 FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

Gene shares homology with the latrophilin-related protein 1 precursor as well as the calcium-independent alpha-latrotoxin receptor. Preferred polypeptide fragments

comprise the following amino acid sequence:

IYKVFRHTAGLKPEVSCFENIRSCARXXXXXXXXXXXXXWIFGVLHVHVASVV  
TAYLFTVSNAFQGMFIFLFLCVLSRKIQEEYYRLFKNPCC (SEQ ID NO:518);  
WIFGVLHVHVASVVTAYLFTVSNAFQGMFIFLFLCVLSRKIQEEYYRLFKNPCC

- 5 C (SEQ ID NO:519). Also preferred are polynucleotide fragments encoding these polypeptide fragments. (See Accession No. 2213659) The translation product of this gene shares sequence homology with CD 97, a seven transmembrane bound receptor.

This gene is expressed primarily in infant brain and in endothelial cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological disorders and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For  
15 a number of disorders of the above tissues or cells, particularly of the neurological and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the  
20 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 294 as residues: Lys-13 to Leu-21.

- The tissue distribution of this gene suggest that it may be useful in the detection and/or treatment of neurodegenerative disease states and behavioral disorders such as  
25 Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder, while its expression in hematopoietic cell types indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma and immunodeficiency diseases.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 62**

This gene is expressed primarily in fetal liver and fetal spleen.

- Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
35 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematological and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes



for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 295 as residues: Ser-91 to Lys-98.

The tissue distribution of this gene fetal liver and spleen indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, leukemia, asthma and immunodeficiency diseases.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 63**

Gene shares homology with human serum amyloid protein. Preferred polypeptide fragments comprise the following amino acid sequence:  
ALTRIPPGDWVINVTAVSFAGKTTARFFHSSPPSLGDQARTDPGHQRRD (SEQ ID NO:520) (See Accession No. W13671). Also preferred are polynucleotide fragments encoding these polypeptide fragments This gene maps to chromosome 9, and therefore, may be used as a marker in linkage analysis for chromosome 9 (See Accession No. AA004342).

This gene is expressed primarily in fetal liver and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematopoietic and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in fetal liver-spleen indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, leukemia, asthma, and immunodeficiency diseases.

#### 5    **FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

This gene maps to chromosome 3, and therefore, may be used as a marker in linkage analysis for chromosome 3 (See Accession No. AA219669).

This gene is expressed specifically in the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurodegenerative disease states. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
15 the above tissues or cells, particularly of the neurological systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the  
20 expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's  
25 Disease, Huntintons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 65**

Gene shares homology with a yeast protein. Preferred polypeptide fragments  
30 comprise the following amino acid sequence: LQEVNITLPENSVWYERYKFDIP VFHL (SEQ ID NO:521). Also preferred are polynucleotide fragments encoding these polypeptide fragments. (See Accession No. 1332638)

This gene is expressed primarily in fetal tissue (fetus and fetal liver).

Therefore, polynucleotides and polypeptides of the invention are useful as  
35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, liver disorders and cancers (e.g. hepatoblastoma). Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 298 as residues: Asn-59 to Glu-64.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 66**

Gene has homology with a B-cell surface antigen which may indicate gene plays a role in the immune response, including, but not limited to disorders and infections of the immune system. Preferred polynucleotide fragments comprise the following sequence: TAGCATGTAGCCAGTCTGAATAACNTATAAGGACAAAGTGGAGTC CACGCGTGC GGCCGTCTAGACTAGTGGATCCCCGGCTGCAGGATTCCGGC ACGAG (SEQ ID NO:523). Also preferred are polypeptide fragments encoded by these polynucleotide fragments (See Accession No.T94535). Additionally, this gene shares homology with an interferon-gamma receptor. Preferred polypeptide fragments also comprise the following amino acid sequence: MQGSGSQFRACLLCLCFSCPC SPGGPRWNSRQGGRFPKTCRAISQNLVFKYKTFCPVRYMQPHRSSLC LHFTS YVFILSTWGLRTYSTDLKKKKNSRGGPVPIRPKS (SEQ ID NO:522); MQGSGSQFRACLLCLCFSCPCSPGGPRWNSRQGGRFPKTCRAISQNLVFK (SEQ ID NO:524); PVRYMQPHRSSLC LHFTSYVFILSTWGLRTYSTDLKKKK NSRGGPVPIRPKS (SEQ ID NO:525); and GEEQRDCSLGWRGVGMRATHCQAA RMFVLFSLPKYAGL (SEQ ID NO:526). Also preferred are polynucleotide fragments encoding these polypeptide fragments

This gene is expressed primarily in T-cells and gall bladder.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunological disorders and conditions (immunodeficiencies, cancer, leukemia, hematopoiesis). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and digestive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 299 as residues: Thr-41 to Gly-52.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of immune disorders including: leukemias, lymphomas, auto-immune disorders, immunosuppressive (transplantation) and immunodeficiencies (e.g. AIDS), inflammation and hematopoietic disorders. The expression of this gene in gall bladder would suggest a possible role for this gene product in digestive disorders, particularly of the pancreas.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 67**

This gene maps to chromosome 11, and therefore, may be used as a marker in linkage analysis for chromosome 11 (See Accession No. AA011622).

This gene is expressed primarily in a variety of fetal and developmental tissues (e.g. fetal spleen, infant brain).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental, immune or neurological abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing immune and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 300 as residues: Ser-38 to Ser-43.

5       The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for developmental abnormalities or fetal deficiencies. The detection in infant brain would suggest a role in neurological disorders (both developmental and neurodegenerative conditions of the brain and nervous system, behavioral disorders, depression, schizophrenia, Alzheimer's disease, Parkinson's  
10       disease, Huntington's disease, mania, dementia). In addition, the detection in spleen would similarly suggest a role in detection and treatment of immunologically mediated disorders (e.g. immunodeficiency, inflammation, cancer, wound healing, tissue repair, hematopoiesis).

#### 15       **FEATURES OF PROTEIN ENCODED BY GENE NO: 68**

      This gene is expressed primarily in spleen, T-cells, and fetal heart.

      Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are  
20       not limited to, immunological deficiencies, including AIDS and cardiovascular disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and cardiovascular systems, expression of this gene at significantly higher  
25       or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30       The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, autoimmune disorders, immunodeficiencies (e.g. AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. The expression in fetal heart indicates that polynucleotides and  
35       polypeptides corresponding to this gene are useful for the treatment and diagnosis of cardiovascular disorders (e.g. heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis).

**FEATURES OF PROTEIN ENCODED BY GENE NO: 69**

Gene shares homology with a human collagen protein. Preferred polypeptide fragments comprise the following amino acid sequence:

- 5 MPRKTSKCRQLLCGASRNADTAARQSTCSSHRPPGKIPSLGPRRXPGCXSV  
SSRGEQSTGSPAAPRCGRRDAHRGLPGGAAMTPGDTWASFNPRAGHSKSQGE  
GQESSGASRQDRHPVSHWVERQREAWGAPRSSSAGGVKVAATTEREPEFKIK  
TGKA (SEQ ID NO:527); CSGASRNADTAARQSTCSSHRPPGKIPSLGPRRXPG  
CXSVPSRGEQSTGSPAAPRCGRRDAHRGLPGGAAMTPGDTWASFNPRAGHS  
10 (SEQ ID NO:528); QGEGQESSGASRQDRHPVSHWVERQREAWGAPRSSSAGG  
VKVAATTEREPEFKIKTGKA (SEQ ID NO:529) (See Accession No. 124886). Also  
preferred are polynucleotide fragments encoding these polypeptide fragments

This gene is expressed primarily in fetal heart.

- Therefore, polynucleotides and polypeptides of the invention are useful as  
15 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, cardiovascular disorders. Similarly, polypeptides and antibodies directed  
to these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
20 tissues or cells, particularly of the cardiovascular system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
such a disorder, relative to the standard gene expression level, i.e., the expression level  
25 in healthy tissue or bodily fluid from an individual not having the disorder. Preferred  
epitopes include those comprising a sequence shown in SEQ ID NO: 302 as residues:  
Pro-32 to Ser-39.

- The tissue distribution indicates that polynucleotides and polypeptides  
corresponding to this gene are useful for the treatment and diagnosis of cardiovascular  
30 disorders (e.g. heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis).

**FEATURES OF PROTEIN ENCODED BY GENE NO: 70**

The translation product of this gene shares sequence homology with a chicken  
single-strand DNA-binding protein. Preferred polypeptide fragments comprise the

- 35 following amino acid sequence:  
MSPRYPGGPRPPLRIPNQUALGGVPGSQPLLPSGMDPTRQQGHPNMGGPMQRM  
TPPRGMVPLGPQNYGGAMRPPLNALGGPGMPGMNMGGGGRPWPNPTNAN

SIPYSSASPGNYVGPPGGGGPPGTPIMPSPADSTNSGDNMYTLMNAVPPGPNR  
 PNFPMPGSDGPMGGLGGMESHMHMNGSLGSGDMDISISKNSPNNMSLSNQP  
 GTPRDDGEMGGNFLNPFQSESYSPSMTMSV (SEQ ID NO:530); MSPRYPGG  
 PRPPLRIPNQALGGVPGSQPLLPSGMDPTRQQGHPNMGGPMQRMTPPRGMVP  
 5 LGPQNYGGAMRPPLNALGGPGMPGMNMGPGGGRPWPNTNANSIPYSSASP  
 GNY (SEQ ID. NO:531); LNALGGPGMPGMNMGPGGGRPWPNTNANSIPYSS  
 ASPGNYVGPPGGGGPPGTPIMPSPADSTNSGDNMYTLMNAVPPGPN (SEQ ID  
 NO:532); GPMGGLGGMESHMHMNGSLGSGDMDISISKNSPNNMSLSNQPGTPR  
 DDGEMGGNFLNPFQSESYSPSMTMSV (SEQ ID NO:533); TCEHSSEAKAFHDY  
 10 (SEQ ID NO:534). Also preferred are polynucleotide fragments encoding these  
 polypeptide fragments. (See Accession No. 1562534)

This gene is expressed primarily in placenta and to a lesser extent in the fetal heart and a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 15 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, developmental abnormalities, fetal deficiencies, and particularly of the  
 cardiovascular system. Similarly, polypeptides and antibodies directed to these  
 polypeptides are useful in providing immunological probes for differential identification  
 20 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
 particularly of the reproductive system, expression of this gene at significantly higher or  
 lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
 tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or  
 another tissue or cell sample taken from an individual having such a disorder, relative to  
 25 the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
 corresponding to this gene are useful for the detection and treatment of developmental  
 abnormalities or fetal deficiencies, ovarian and other endometrial cancers, reproductive  
 30 dysfunction, cardiovascular disorders, and pre-natal disorders.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 71

This gene is expressed primarily in fetal liver and to a lesser extent in the breast and testes.

35 Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, liver disorders (including hepatoblastomas) and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). The expression in testes and breast indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of endocrine and reproductive disorders (e.g. sperm maturation, milk production, testicular and breast cancers).

## **20 FEATURES OF PROTEIN ENCODED BY GENE NO: 72**

This gene maps to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1 (See Accession No. W93595).

This gene is expressed primarily in smooth muscle and to a lesser extent in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cardiovascular and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiovascular and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.



The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of restenosis, atherosclerosis, stroke, angina, thrombosis, wound healing and other conditions of heart disease. In addition, the expression in brain would suggest that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of developmental, degenerative and behavioral conditions of the brain and nervous system (e.g. schizophrenia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and sleep disorders).

### FEATURES OF PROTEIN ENCODED BY GENE NO: 73

Gene shares homology with human stromalin-2. Preferred polypeptide fragments comprise the following amino acid sequence:

QAFVLLSLLLLIFSPQMIVGGRDFLRPLVFFPEATLQSELASFLMDHVFIQPGDL  
 GSGA (SEQ ID NO:535); ACSYLLCNPEFTFFSRADFARSQLVDLLTDRFQQE  
 LEELLQVG (SEQ ID NO:536), QKQLSSLRDRMVAFCELCQSCLSDVDTEIQEQV  
 ST (SEQ ID NO:537); QVILPALTLVYFSILWTLTHISKSDAS (SEQ ID NO:538);  
 STHDLTRWELYEPCQLLQKAVDTGXVPHQV (SEQ ID NO:539). Also preferred  
 are polynucleotide fragments encoding these polypeptide fragments (See Accession  
 No.R65208 ) This gene maps to chromosome 7, and therefore, may be used as a  
 marker in linkage analysis for chromosome 7 (See Accession No. D52585).

This gene is expressed primarily in the brain (infant brain, adult brain, pituitary, cerebellum, hippocampus, schizophrenic hypothalamus, amygdala).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those

comprising a sequence shown in SEQ ID NO: 306 as residues: Thr-25 to Lys-36, Lys-55 to Ser-63.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection and treatment of developmental, degenerative and behavioral conditions of the brain and nervous system (e.g. schizophrenia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior and sleep disorders).

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 74**

This gene is expressed primarily in the hypothalamus of a human suffering from schizophrenia.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders of the CNS particularly schizophrenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, such as schizophrenia expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 307 as residues: Gly-38 to Ala-44.

The tissue distribution indicates that the protein products of this gene are useful for the study, diagnosis and treatment of schizophrenia and other disorders involving the CNS.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 75**

Preferred polypeptides of the invention comprise the following amino acid sequence encoded by this gene:

LAVSTSFICCADISTALPLGSSRPAPAPRHREHEHGHQARPPRLX TSLMPLSTP  
AAQQLWTQLTPMGGRPGGRHSPTLHTGPRALPPGPPHPSLHVAALSLLR

(SEQ ID NO:540). Polynucleotides encoding such polypeptides are also provided.

This gene is expressed primarily in endometrial tumor and to a lesser extent in amniotic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, reproductive and immune disorders particularly cancers of those systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 308 as residues: Ser-3 to Arg-9.

The tissue distribution indicates that the protein products of this gene are useful for study and treatment of immune and reproductive disorders particularly cancers of those systems.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 76**

This gene is expressed primarily in kidney cortex and to a lesser extent in early stage human brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, renal disorders such as renal cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the kidney expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 309 as residues: Gly-38 to Gly-45, Gly-47 to Gly-52, Pro-92 to Lys-110.

The tissue distribution indicates that the protein products of this gene are useful for study, treatment and diagnosis of renal diseases such as cancer of the kidney.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 77**

This gene is expressed primarily in kidney medulla.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, metabolic and renal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
10 the above tissues or cells, particularly of the metabolic and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
15 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for study, treatment and diagnosis of metabolic and renal diseases and disorders.

**20 FEATURES OF PROTEIN ENCODED BY GENE NO: 78**

This gene is expressed in chronic synovitis and microvascular endothelium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are  
25 not limited to, arthritis and atherosclerosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and skeletal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain  
30 tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35 The tissue distribution indicates that the protein products of this gene are useful for study, diagnosis and treatment of arthritic and other inflammatory diseases as well as cardiovascular diseases.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 79**

This gene is expressed in resting T-cells and activated monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, immune disorders. Similarly, polypeptides and antibodies directed to  
these polypeptides are useful in providing immunological probes for differential  
10 identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the immune system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
such a disorder, relative to the standard gene expression level, i.e., the expression level  
15 in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful  
for the study and treatment of immune diseases such as inflammatory conditions.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 80**

20 This gene is expressed in a variety of immune system tissues, e.g., neutrophils,  
T-cells, and TNF induced epithelial and endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
25 not limited to, infectious and immune disorders. Similarly, polypeptides and antibodies  
directed to these polypeptides are useful in providing immunological probes for  
differential identification of the tissue(s) or cell type(s). For a number of disorders of  
the above tissues or cells, particularly of the immune and vascular systems, expression  
of this gene at significantly higher or lower levels may be routinely detected in certain  
30 tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,  
urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID  
35 NO: 313 as residues: Met-1 to Trp-6.

The tissue distribution indicates that the protein products of this gene are useful  
for study and treatment of infectious diseases, immune and vascular disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 81**

This gene is expressed in activated neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, inflammation and other immune conditions. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
10 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the immune system, expression of this gene  
at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
15 such a disorder, relative to the standard gene expression level, i.e., the expression level  
in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful  
for study and treatment of immune disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 82**

20 This gene is expressed in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, inflammatory and other immune conditions. Similarly, polypeptides and  
25 antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the immune system, expression of this gene  
at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
30 fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
such a disorder, relative to the standard gene expression level, i.e., the expression level  
in healthy tissue or bodily fluid from an individual not having the disorder. Preferred  
epitopes include those comprising a sequence shown in SEQ ID NO: 315 as residues:  
Ala-83 to Thr-91.

35 The tissue distribution indicates that the protein products of this gene are useful  
for study and treatment of immune disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 83**

This gene is expressed in human neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, inflammation and immune disorders. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
10 of the above tissues or cells, particularly of the immune and inflammatory system,  
expression of this gene at significantly higher or lower levels may be routinely detected  
in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum,  
plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from  
an individual having such a disorder, relative to the standard gene expression level, i.e.,  
15 the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

The tissue distribution indicates that the protein products of this gene are useful  
for diagnosis and treatment of disorders of the inflammatory and immune systems.

**20 FEATURES OF PROTEIN ENCODED BY GENE NO: 84**

This gene is expressed in human neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
25 not limited to, disorders of the inflammatory and immune systems. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
immunological probes for differential identification of the tissue(s) or cell type(s). For  
a number of disorders of the above tissues or cells, particularly of the inflammatory and  
immune systems, expression of this gene at significantly higher or lower levels may be  
30 routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily  
fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or  
cell sample taken from an individual having such a disorder, relative to the standard  
gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
individual not having the disorder.

35 The tissue distribution indicates that the protein products of this gene are useful  
for diagnosis and treatment of disorders of the immune and inflammatory systems.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 85**

This gene is expressed in activated neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, inflammation and immune system diseases. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
10 of the above tissues or cells, particularly of the immune system and inflammatory  
system, expression of this gene at significantly higher or lower levels may be routinely  
detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g.,  
serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample  
taken from an individual having such a disorder, relative to the standard gene  
15 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful  
for diagnosis and treatment of diseases of the inflammatory and immune systems.

**20 FEATURES OF PROTEIN ENCODED BY GENE NO: 86**

This gene is expressed in activated neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
25 not limited to, inflammation and immune system disorders. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the inflammatory and immune system,  
expression of this gene at significantly higher or lower levels may be routinely detected  
30 in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum,  
plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from  
an individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID  
35 NO: 319 as residues: Met-1 to Gly-6, Gly-32 to Pro-43, Leu-55 to Gln-60.

The tissue distribution indicates that the protein products of this gene are useful  
for diagnosis and treatment of disorders of the immune and inflammatory system.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 87**

In specific embodiments, polypeptides of the invention comprise the sequence:  
 EQVLALLWPRFELILEMNVQSVRSTDPQRLGGLDTRPHYTTRRYAEFSSALVSIN  
 5 QTIPNERTMQLLGQLQVEVENFVLRVAAEFSSRKEQLVFLINNYDMMLGVLME  
 RAADDSEVESFQQLLNARTQEFIEELLSPFPGGLVAFVKEAEALIERGQAERLR  
 GEEARVTQLIRFGSSWKSSVESLSQDVMRSFTNFRNGTSIIQG (SEQ ID  
 NO:541), ALLKYRFFYQFLGNERATAKEIRDEYVETLSKIYLSYYRSYLGRMLK  
 VQYEEVAEKDDLGMVEDTAKKGFXXSKPSRSRNTIFTLGTRGSVISPTELEAPILV  
 10 PHTAQR (SEQ ID NO: 542); EQRYPFALFRSQHYXLLDNSCREYLFICEFFVVS  
 GPXAHDLFHAVMGRTLSMTLKHLDSYLADCYDAIAVFLCIHIVLRFRNIAAKRD  
 VPALDRYW (SEQ ID NO:543), GGLDTRPHYTTRRYAEFSSALVSINQ (SEQ ID  
 NO:544); SRKEQLVFLINNYDMMLGVL (SEQ ID NO: 545) and/or ALLKYRFFY  
 QFLGNERATAKEIRDEYVETLSKIYLSYYRSYLGRMLKVQYEEVAEKDDLGMG  
 15 VEDTAKKGFXXSKPSLSRNTIFTLGTRGSVISPTELEAPILVPHTAQRXEQRYPF  
 EALFRSQHYXLLDNSCREYLFICEFFVVS GPXAHDLFHAVMGRTLSMTLKHLDSYLADCYDAIAVFLCIHIVLRFRNIAAKRDVPALDRYWEQVLALLWPRFELILEM  
 NVQSVRSTDPQRLGGLDTRPHYTTRRYAEFSSALVSINQTIPNERTMQLLGQLQV  
 EVENFVLRVAAEFSSRKEQLVFLINNYDMMLGVL MERAADDSEVESFQQLLN  
 20 ARTQEFIEELLSPFPGGLVAFVKEAEALIERGQAERLRGEEARVTQLIRFGSSW  
 KSSVESLSQDVMRSFTNFRNGTS (SEQ ID NO:546). Polynucleotides encoding  
 these polypeptides are also encompassed by the invention. The translation product of  
 this gene shares sequence homology with suppressor of actin mutation which is thought  
 to be important in mutation suppression.

25 This gene is expressed primarily in fetal liver and to a lesser extent in a variety  
 of other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 30 not limited to, liver and mutations. Similarly, polypeptides and antibodies directed to  
 these polypeptides are useful in providing immunological probes for differential  
 identification of the tissue(s) or cell type(s). For a number of disorders of the above  
 tissues or cells, particularly of the liver or cancer, expression of this gene at  
 significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
 35 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
 fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
 such a disorder, relative to the standard gene expression level, i.e., the expression level

in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 320 as residues: Val-53 to Arg-60, Thr-88 to Thr-94, Ala-142 to Ser-150, Gly-188 to Glu-196, Gly-208 to Ser-214, Thr-227 to Gly-232, Lys-279 to Phe-285.

- 5 The tissue distribution and homology to suppressor of actin mutation suggest that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and of liver disorder or cancer.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 88

- 10 This gene maps to chromosome 9, and therefore can be used in linkage analysis as a marker for chromosome 9. In specific embodiments, polypeptides of the invention comprise the sequence:

- YEGKEFDYVFSIDVNEGGPSYKLPYNTSDDPWLTAYNFLQKNDLNPMFLDQVA  
KFIIDNTKGQMLGLGNPSFSDPFTGGGRYVPGSSGSSNTLPTADPFTGAGRYV  
15 PGSASMGTTMAGVDPFTGNSAYRSAASKTMNIYFPKKEAVTFDQANPTQILGK  
LKELNGTAPEEKLTEDDLILLEKILSLICNSSSEKPTVQQQLQILWKAINCPEDIV  
FPALDILRLSIKHPSVNENFCNEKEGAQFSSHLINLLNPKGKPANQLLALRTFC  
NCFVGQAGQKLMMSQRESLSHAIELKSGSNKNI (SEQ ID NO: 547);  
HIALATLALNYSVCFHKD (SEQ ID NO: 548); HNIEGKAQCLSLISTILEVVQ  
20 DLEATFRLLVALGTLISDDSNVQLAKS (SEQ ID NO:549); LGVDSQIKKYSS  
VSEPAKVSECCRFILNLL (SEQ ID NO:550); and/or YEGKEFDYVFSIDVNEGGPS  
YKLPYNTSDDPWLTAYNFLQKNDLNPMFLDQVAKFIIDNTKGQMLGLGNPSFS  
DPFTGGGRYVPGSSGSSNTLPTADPFTGAGRYVPGSASMGTTMAGVDPFTGN  
SAYRSAASKTMNIYFPKKEAVTFDQANPTQILGKLKELNGTAPEEKLTEDDLI  
25 LLEKILSLICNSSSEKPTVQQQLQILWKAINCPEDIVFPALDILRLSIKHPSVNENFC  
NEKEGAQFSSHLINLLNPKGKPANQLLALRTFCNCFVGQAGQKLMMSQRESL  
MSHAIELKSGSNKNIHIALATLALNYSVCFHKDHNIEGKAQCLSLISTILEVVQD  
LEATFRLLVALGTLISDDSNVQLAKSLGVDSQIKKYSSVSEPAKVSECCRFILN  
LL (SEQ ID NO:551). Polynucleotides encoding these polypeptides are also  
30 encompassed by the invention. These polypeptides share significant homology with  
phospholipase A2 activating protein which is thought to be important in signal  
transduction (see, e.g., Wang et al., Gene 161(2):237-241 (1995)).

- This gene is expressed primarily in endothelial cells, to a less extent in placenta,  
endometrial stromal cells, osteosarcoma, testis tumor, muscle, and infant brain that are  
35 likely to be rich in blood vessels.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders in vascular system, aberrant angiogenesis, tumor angiogenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system or tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in endothelial cells and several potential highly vascularized tissues and its homology to phospholipase A2 activating protein suggest that this gene may be involved in transducing signals for endothelial cells in angiogenesis or vasculogenesis.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 89

In specific embodiments, polypeptides of the invention comprise the sequence: YPNQDGDILRDQVLHEHIQRLSKVVTANHRALQIPEVYLREAPWPSAQSEIRTIS AYKTPRDKVQCILRMCSTIMNLLSLANEDSVPGADDFVPVLVFLIKANPPCLLSTVQYISSFYASCLSGEESYWWMQFTA AVE (SEQ ID NO:552); YPNQDGDILRDQVLHEHIQRLSKVVTANHRALQIPEVYLREAPWPSAQSEIRTISAYKTPRDKVQCILRMCSTIMNLLSLANEDSVPGADDFVPVLVFLIKANPPCLLSTVQYISSFYASCLSGEESYWWMQFTA AVEFIKTI (SEQ ID NO:553); YPNQDGDILRDQVL (SEQ ID NO:554); EAPWPSAQSEI (SEQ ID NO:555); PVLVFLIKANP (SEQ ID NO:560); SGEESYWWMQFTA AVEFIKTI (SEQ ID NO:556); ADDDFVPVLVFLIKANPP (SEQ ID NO:557); YKTPRDKVQCIL (SEQ ID NO:558); and/or GADDFVPVLVFLIK (SEQ ID NO:559). The translation product of this gene shares sequence homology with human ras inhibitor and yeast VPS9p which is thought to be important in golgi vacuole transport.

This gene is expressed primarily in T cells and melanocytes and to a lesser extent in a variety of other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, dysfunction and disorders involving T cells and melanocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to ras inhibitor indicates that polynucleotides and polypeptides corresponding to this gene are useful for regulating signal transduction; diagnosis and treatment of disorders involving T cells and melanocytes.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 90**

This gene maps to chromosome 9 and therefore polypeptides of the invention can be used in linkage analysis as a marker for chromosome 9. The translation product of this gene shares sequence homology with neuronal olfactomedin-related ER localized protein which is thought to be important in influence the maintenance, growth, or differentiation of chemosensory cilia on the apical dendrites of olfactory neurons. In specific embodiments, polypeptides of the invention comprise the sequence: SARASTQPPAGQHGPC (SEQ ID NO:561); MPGRWRWQRDMHPARKLLSLL FLILMGTELTQD (SEQ ID NO:562); SAAPDSLLRSSKGSTRGSL (SEQ ID NO:563); AAIVIWRGKSESRIAKTPGI (SEQ ID NO:564); FRGGGTLVLPPTHT PEWLIL (SEQ ID NO:567); PLGITLPLGAPETGGGD (SEQ ID NO:565); and/or CAAETWKGSQRAGQLCALLA (SEQ ID NO:566).

This gene is expressed in pineal gland.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological and endocrinological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological or endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 323 as residues: Leu-20 to Ala-26, Arg-32 to Arg-39, Thr-104 to Gly-112.

5 The tissue distribution and homology to olfactomedin-related protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for maintenance, growth, or differentiation of neuron cells in pineal gland, therefore, may be useful for diagnosis and treatment of neurological disorders in pineal gland.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 91**

10 This gene is expressed primarily in prostate and apoptotic T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, prostate disease and T cell dysfunction. Similarly, polypeptides and  
15 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate cancer, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
20 fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for detect abnormal activity in prostate and T cells  
25 or probably treatment of this abnormality.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 92**

This gene is expressed primarily in prostate and to a lesser extent in smooth muscle cells, fibroblasts, and placenta.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders in prostate or vascular system. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
35 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate or vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain

tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for regulating function of prostate or highly vascularized tissues, e.g. placenta.

#### 10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 93**

This gene is expressed primarily in embryos and fetal tissues stage human and to a lesser extent in a wide variety of other proliferative tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders in embryonic development and cell proliferation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the embryonic tissues and proliferative cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis or treatment of abnormalities in developing and proliferative cells and organs.

#### 30 **FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

The translation product of this gene shares sequence homology with transformation related protein which is thought to be important in transformation.

This gene is expressed primarily in female reproductive tissues, i.e., breast cancer cells, placenta, and ovary and to a lesser extent in fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, cancer or dysfunction of reproductive tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproduction system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 327 as residues: Ser-50 to Pro-61.

The tissue distribution and homology to transformation related protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of conditions caused by transformation, i.e. tumorigenesis in reproductive organs, e.g. breast, placenta, and ovary.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 95**

This gene is expressed primarily in testes, rhabdomyosarcoma, infant brain and to a lesser extent in some tumors and highly vascularized tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, tumorigenesis, abnormal angiogenesis, and/or neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor tissues or vascular tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 328 as residues: Arg-46 to Trp-54, Pro-60 to Ile-69, Asn-116 to Ala-122, Arg-147 to Lys-153, Ser-158 to Glu-170, Ile-399 to Ser-405, Pro-486 to Met-499, Pro-502 to Asp-508.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for a range of disease states including treatment of

tumor or vascular disorders and the treatment of neurological disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

**5 FEATURES OF PROTEIN ENCODED BY GENE NO: 96**

This gene maps to chromosome 7 and therefore polynucleotides of the present invention can be used in linkage analysis as a marker for chromosome 7. The translation product of this gene is homologous to the *Clostridium perfringens* enterotoxin (CPE) receptor gene product and shares sequence homology with a human ORF specific to prostate and a glycoprotein specific to oligodendrocytes both of which are tissue specific proteins. (See e.g., Katahira et al., J Cell Biol. 136(6):1239-1247 (1997). PMID: 9087440; UI: 97242441.

This gene is expressed primarily in pancreas tumor and ulcerative colitis and to a lesser extent in several tumors and normal tissues.

15 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, pancreatic disorder, ulcerative colitis, tumors and food poisoning. Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
20 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system or tumorigenic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal  
25 fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 329 as residues: Gly-147 to Met-152, Cys-177 to Lys-188.

30 The tissue distribution and homology to prostate and oligodendrocyte-specific protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for marker of diagnosis or treatment of disorder in pancreas, ulcerative colitis, and tumors. Furthermore, identity to the human receptor for *Clostridium perfringens* enterotoxin indicates that the soluble portion of this receptor could be used in the  
35 treatment of food poisoning associated with *Clostridia perfringens* by blocking the activity of perfringens enterotoxin.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 97**

The translation product of this gene shares sequence homology with ATPase which is thought to be important in metabolism.

- 5 This gene is expressed primarily in testes and several hematopoietic cells and to a lesser extent in other tissues.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, leukemia and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 330 as residues: Leu-37 to Ala-42.

The tissue distribution and homology to ATPase indicates that polynucleotides and polypeptides corresponding to this gene are useful for marker of diagnosis and treatment of leukemia and other hematopoietic disorders.

**25 FEATURES OF PROTEIN ENCODED BY GENE NO: 98**

In specific embodiments, polypeptides of the invention comprise the sequence: MRSARPSLGCLPSWAFSQALNI (SEQ ID NO:568); LLGLKGLAPAEISAVCE KGNFN (SEQ ID NO:569); VAHGLAWSYYIGYLRLLPELQARIR (SEQ ID NO:570); TYNQHYNLLRGAVSQRC (SEQ ID NO:571); ILLPLDCGVPDNLSM ADPNIRFLDKLPQQTGDRAGIKDRVYSN (SEQ ID NO:572); SIYELLENGQRAGT CVLEYATPLQTLFAMSQYSQAGFSGEDRLEQ (SEQ ID NO:573); AKLFCRTLE DILADAPESQNNCRLIA YQEPADDSSFSLSQEVLRHLRQEEKEEVTGSLKTS AV PSTSTMSQEPPELLISGMEKPLPLRTDFS (SEQ ID NO:574); and/or LLGLKGLA PAEISAVCEKGNFNVAHGLAWSYYIGYLRLLPEL (SEQ ID NO:575).

- 35 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in prostate BPH and to a lesser extent in bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, benign prostatic hypertrophy or prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male urinary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 331 as residues: Ile-60 to Asn-69, Leu-106 to Asp-112, Glu-130 to Gly-136, Phe-160 to Glu-167, Pro-184 to Cys-190, Glu-197 to Ser-202, Arg-215 to Glu-221, Thr-237 to Pro-242.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis or treatment of benign prostatic hypertrophy or prostate cancer.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 99

This gene is expressed primarily in salivary gland.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders or injuries of the salivary gland. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of glandular tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of disorders of, or injuries to the salivary gland or other glandular tissue.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 100**

This gene maps to chromosome 15, accordingly, polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 15. The translation product of this gene shares sequence homology with a *C.elegans* gene of unknown function. In specific embodiments, polypeptides of the invention comprise the sequence: DPRVRLNSLTCKHIFISLTQ (SEQ ID NO:583); TMKLLKLRRNIV KLSLYRHFTN (SEQ ID NO:576); TLILAVAASIVFIWTTMKFRI (SEQ ID NO:577); VTCQSDWRELWVDDAIWRLLFSMILFVI (SEQ ID NO:578); MVLWR PSANNQRFAFSPLSEEEEEDEQ (SEQ ID NO:580); KEPMLKESFEGMKMRS TKQEPNGNSKVNKAQEDDL (SEQ ID NO:584); and/or KWVEENVPSVTDVALP ALLDSDEERMITHFERSKME (SEQ ID NO:582). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in thyroid and to a lesser extent in osteoclastoma, kidney medulla, and lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, thyroid dysfunction or cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 333 as residues: Lys-107 to Leu-124, Glu-150 to Thr-159, Pro-173 to Asp-179, Ser-192 to Ser-201.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of thyroid dysfunction or cancer.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 101**

This gene maps to chromosome 16, therefore polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 16. In specific embodiments, polypeptides of the invention comprise the sequence:

IRHELTVLRDTRPACA (SEQ ID NO:585); and/or MDFXMALIYD (SEQ ID NO:586). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in kidney cortex and to a lesser extent in adult brain, corpus colosum, hippocampus, and frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to  
10 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
15 fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment or diagnosis of neurological  
20 disorders.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 102

In specific embodiments, polypeptides of the invention comprise the sequence:  
MQEMMRNQDRALSNLESIPGGYNA (SEQ ID NO:587); LRRMYTDIQEPMLSA  
25 AQEQF GGNPF (SEQ ID NO:588); ASLVSNNTSSGEGSQPSRTENRDPLPNWAP  
QT (SEQ ID NO:589); SQSSASSGTASTVGGTTGSTASGTSGQSTTAPNLVPGV  
GASMFNTPG MQSLLQQITENPQLMQNMLSAPY (SEQ ID NO:590);  
MRSMMQSLSQNPDLAAQMMLNNPLFAGNPQLQEQMRQQLPTFLQQ (SEQ ID  
NO:591); MQNPDTLSAMSNPRAMQALLQIQGLQTLATEAPGLIPGFTPGLG  
30 ALGSTGGSSGTNGSNATPSENTSPTAGT (SEQ ID NO:592); TEPGHQQFI  
QQMLQALAGVNPQLQNPEVRFQQQLEQLSAMGFLNREANLQALATGGDINAA  
IERLLGSQPS (SEQ ID NO:593); RNPAMMQEMMRNQDRALSNLESIPGGY  
NALRRMYTDIQEPMLSAA (SEQ ID NO:594); GNPFASLVSNNTSS (SEQ ID  
NO:595); ENRDPLPNPWA (SEQ ID NO:595); GKILKDQDTLSQHGHD (SEQ ID  
35 NO:597); GLTVHLVIKTQNRP (SEQ ID NO:598); SELQSQMQRQLLSNPEMM  
(SEQ ID NO:599); PEISHMLNNPDIMR (SEQ ID NO:600); and/or  
RQLIMANPQMQLIQRNP (SEQ ID NO:601). Polynucleotides encoding these

polypeptides are also encompassed by the invention.

This gene is expressed primarily in breast.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of tumor systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of some types of breast cancer.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 103**

The translation product of this gene shares sequence homology with secreted serine proteases and lysozyme C precursor, which is thought to be important in bacteriolytic function. In specific embodiments, polypeptides of the invention comprise the sequence: NLCHVDCQDLLNP NLLAGIHCAKRIVS (SEQ ID NO:602); LDGFEGYSLSDWLCLAFVESKFN (SEQ ID NO:603); NENADGSFDYGLFQINSHYWCN (SEQ ID NO:604); and/or NLCHVDCQDLLNP NLLAGIHCAKRIVS (SEQ ID NO:605). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, infection. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 336 as residues: Ile-62 to Phe-70, Asn-78 to Asn-84.

The tissue distribution and homology to lysozyme C precursor indicates that polynucleotides and polypeptides corresponding to this gene are useful for boosting the monocyte-macrophage system and enhance the activity of immunoagents.

#### 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 104

This gene is expressed primarily in apoptotic T-cell.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of some immune disorders.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 105

The translation product of this gene shares sequence homology with ARI protein of Drosophila (accession: 2058299; EMBL: locus DMARIADNE, accession X98309), which is thought to be important in axonal path-finding in the central nervous system. In specific embodiments, polypeptides of the invention comprise the sequence IREVNEVIQNPA-T (SEQ ID NO:606); ITRILLSHFNWDKEKLMERYF DGNLEKLFA (SEQ ID NO:607); NTRSSAQDMPQCICYLNYPNSYF (SEQ ID NO:608); TGLECGHKFCMQCWSEYLTTKIMEEGMGQTISCPAHG (SEQ ID NO:614); CDILVDDNTVMRLITDSKVKLKYQHLITNSFVECNRLWKWCPAPD CHHVVKVQYPDAKPV (SEQ ID NO:609); CDILVDDNTVMRLITDSK

VKLKYQHLITNSFVECNRLWKWCPAPDCHHVVKV (SEQ ID NO:610);  
 GCNHMVCRNQNCCKAEFCWVCLGPWEPHGSAWYNCNRYNEDDAKAARDAQE  
 RSRAALQRYL (SEQ ID NO:611); FYCNRYMNHMQSLRFEHKLYAQVKQ  
 KMEEMQQHNMSWIEVQFLKKAVDVLCQCRATLMYT (SEQ ID NO: 612);  
 5 YVFAFYLKNNQSIIFENNQADLENATEVLSGYLERDISQDSLQDIKQKVQDKY  
 RYCESR (SEQ ID NO:613) Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

This gene is expressed primarily in adult brain, and to a lesser extent in  
 endometrial tumor, melanocytes, and infant brain.

10 Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, diseases or injuries involving axonal path development. Similarly,  
 polypeptides and antibodies directed to these polypeptides are useful in providing  
 15 immunological probes for differential identification of the tissue(s) or cell type(s). For  
 a number of disorders of the above tissues or cells, particularly of the central nervous  
 system, expression of this gene at significantly higher or lower levels may be routinely  
 detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g.,  
 serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample  
 20 taken from an individual having such a disorder, relative to the standard gene  
 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 individual not having the disorder.

The tissue distribution and homology to ARI protein indicates that  
 polynucleotides and polypeptides corresponding to this gene are useful for treatment of  
 25 disease states or injuries involving axonal path development, including  
 neurodegenerative diseases and nerve injury.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 106**

The translation product of this gene shares sequence homology with cytochrome  
 30 b561 [Sus scrofa] which is thought to be an integral membrane protein of  
 neuroendocrine storage vesicles of neurotransmitters and peptide hormones.

This gene is expressed primarily in frontal cortex and to a lesser extent in  
 rhabdomyosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 35 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to

these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 339 as residues: Ser-18 to Pro-24.

The tissue distribution and homology to cytochrome b561 [*Sus scrofa*] indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of neurological disorders. This gene may also be important in regulation of some types of cancers.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 107

In specific embodiments, polypeptides of the invention comprise the sequence: MWGYLFDVDAAWNFLGCLICGW (SEQ ID NO:615); MHFISSGNVSAIRSSILLRXSLSYLGNCRLRVSAIFVYFLLFLLLS (SEQ ID NO:616); and/or MDQALRGSPSEGFSTDPSPPQVGRQIPSFPPWRRLLVLPKASGCFLEREWLWLCVFKLRTRPGAEEAHAYNSSILGGRGKGIT (SEQ ID NO:617). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in pancreas tumor and to a lesser extent in cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, pancreatic tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred



epitopes include those comprising a sequence shown in SEQ ID NO: 340 as residues: Pro-22 to Phe-33.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of pancreatic tumors.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 108

This gene maps to chromosome 17 and therefore polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 17. In specific embodiments, polypeptides of the invention comprise the sequence:

10 MLPALASCCHFSPPEQAARLKKLQEQEKQKVEFRKRMEKEVSDFIQDSGQIK  
KKFQPMNKIERSILHDVVEVAGLTSFSFGEDDDCRYVMIFKKEFAPSDEELDSY  
RRGEEWDPQKAEEKRNXXKELAQRR (SEQ ID NO:618); EEEAAQQGPVVV  
SPASDYKDKYSHLIGKGAAKDAAHMLQANKTYGCXPVANKRDTRSIEEAMNE  
IRAKKRLRQSGE (SEQ ID NO:619); PPRRPAQLPLTPGAGQGAGRDKAAAIRA  
15 HPGAPPLNHLLP (SEQ IDNO:620); AVPQAGGKQVFDLSPLELGYVRGMCVCV  
(SEQ ID NO:621) and/or MLPALASCCHFSPPEQAARLKKLQEQEKQKVEFRK  
RMEKEVSDFIQDSGQIKKKFQPMNKIERSILHDVVEVAGLTSFSFGEDDDCRYV  
MIFKKEFAPSDEELDSYRRGEEWDPQKAEEKRNXXKELAQRRQEEAAQQGPVVV  
SPASDYKDKYSHLIGKGAAKDAAHMLQANKTYGCXPVANKRDTRSIEEAMNE  
20 IRAKKRLRQSGE (SEQ ID NO:622). Polynucleotides encoding these polypeptides  
are also encompassed by the invention. The translation product of this gene shares  
sequence homology with FSA-1 which may play a role as a structural protein  
component of the acrosome.

This gene is expressed primarily in fetal kidney and sperm.

25

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, male reproductive disorders, especially involving acrosomal disfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
30 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or  
35 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an

individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 341 as residues: Glu-8 to Asn-35.

The tissue distribution and homology to FSA-1 indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of infertility due to  
5 acrosomal dysfunction of sperm.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 109**

This gene is expressed primarily in pituitary and to a lesser extent in epididymus.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, male reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
15 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an  
20 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 342 as residues: Met-1 to Trp-6.

Because the gene is found in both pituitary and epididymus, this indicates that  
25 polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of male reproductive disorders. This may involve a secreted peptide produced in the pituitary targeting the epididymus.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 110**

30 In specific embodiments, polypeptides of the invention comprise the sequence: LLCPLVNSGXSWNFPHPSPQEYSFHGFHSTRLWI (SEQ ID NO:623); and/or PSTPWFLFLLGLTCPFSTSHPRWDSIPP (SEQ ID NO:624). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in resting T-cells. .

35 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, T-cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of certain immune disorders, especially those involving T-cells.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 111**

This gene is expressed primarily in cerebellum and whole brain and to a lesser extent in infant brain and fetal kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 344 as residues: Asp-48 to Gly-55.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurological disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 112**

The translation product of this gene shares sequence homology with yeast mitochondrial ribosomal protein homologous to ribosomal protein s15 of E.coli which

is thought to be important in the early assembly of ribosomes (See Accession No. M38016). This gene maps to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in developmental tissues.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, development of cancers and tumors in addition to healing wounds. Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
10 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or  
15 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to ribosomal protein s15 of *E. coli* indicates that polynucleotides and polypeptides corresponding to this gene are useful for  
20 diseases related to the assembly of ribosomes in the mitochondria which is important in the translation of RNA into protein. Therefore, this indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of multiple tumors as well as in healing wounds which are thought to be under similar regulation as developmental tissues. Protein, as well as, antibodies directed against the  
25 protein have utility as tumor markers, in addition to immunotherapy targets, for the above listed tumors and tissues.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 113**

The translation product of this gene shares sequence homology with human  
30 poliovirus receptor precursors which are thought to be important in viral binding and uptake. Preferred polypeptide fragments comprise the following amino acid sequence:  
ELISISNVALADEGEYTCISFTMPVRTAKSLVTVLGIPQKPIITGYKSSLREKDT  
ATLNCQSSGSKPAARLTWRKGDQELHGEPTRIQEDPNGKTFTVSSSVTFQVTR  
EDDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPDPPHPREGQKLLLHC  
35 EGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCTATSNMG  
YKAYYTLNVND (SEQ ID NO:625). Also preferred are polynucleotide fragments encoding these polypeptide fragments (See Accession No. gnllPID1d1002627).

This gene is expressed almost exclusively in human brain tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, susceptibility to viral disease and diseases of the CNS especially cancers of that system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 346 as residues: Leu-26 to Asp-37, Lys-53 to Ser-59.

The tissue distribution and homology to poliovirus receptor precursors indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and prevention of diseases that involve the binding and uptake of virus particles for infection. It might also be helpful in genetic therapy where the goal is to insert foreign DNA into infected cells. With the help of this protein, the binding and uptake of this foreign DNA might be aided. In addition, it is expected that over expression of this gene will indicate abnormalities involving the CNS, particularly cancers of that system.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 114**

The translation product of this gene shares sequence homology with YO87\_CAEEL hypothetical 28.5 KD protein ZK1236.7 in chromosome III of *Caenorhabditis elegans* in addition to alpha-1 collagen type III (See Accession No. gi537432). One embodiment for this gene is the polypeptide fragment(s) comprising the following amino acid sequence: VPELPDRVHQLHQA VQGCGALGRPGFPGGPTH SGHHKSHPGPAGGDYNRCDRPGQVHLHNPRGTGRRGQLHPTAGPGVHRRACPSQQLPHRLGPGVPCPSLTPVLPSWTQSWCG LPGYTSSS (SEQ ID NO:630). An additional embodiment is the polynucleotide fragment(s) encoding these polypeptide fragments

This gene is expressed primarily in brain cells and to a lesser extent in activated B and T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurodegeneration and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 347 as residues: Glu-34 to Glu-39, Gly-51 to Ser-72, Ala-88 to Glu-93, Gln-100 to Val-105.

The tissue distribution and homology to YO87\_CAEEL hypothetical 28.5 KD protein ZK1236.7 in chromosome III of *Caenorhabditis elegans* as well as to a conserved alpha-1 collagen type III protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons' Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorders. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 115**

The translation product of this gene shares sequence homology with alpha 3 type IX collagen which is thought to be important in hyaline cartilage formation via its ability to uptake inorganic sulfate by cells (See Accession No. gi1975657). One embodiment of this gene is the polypeptide fragment comprising the following amino acid sequence: SLRRPRSAAXQTLLTFLSSVSSASSALPGSREPCDPRAPPPRR SGSAASCCSCCSCPRRRAPLRSPRGSKRRIRQREVVDLYNGMCLQGPAGVPG RDGSPGANGIPGTPGIPGRDGFKGKGECLRESFEESWTPNYKQCSWSSLNY GIDLGKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGP LPIEAIYLDQGSPEMNSTINIHRITSSVEGLCEGIGAGLVDVAIWVGTCSDYPKG DASTGWNSVSRIIIIEELPK (SEQ ID NO:634). An additional embodiment are the

polynucleotide fragments encoding this polypeptide fragment.

This gene is expressed primarily in smooth muscle and to a lesser extent in synovial tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e., spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid and autoimmune  
10 disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily  
15 fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to alpha 3 type IX collagen indicates that  
20 polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of diseases associated with the mutation in this gene which leads to the many different types of chondrodysplasias. By the use of this product, the abnormal growth and development of bones of the limbs and spine could be routinely detected or treated in utero since the protein or mutants thereof could affect epithelial cells early in  
25 development and later the chondrocytes of the developing craniofacial structure.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 116**

The translation product of this gene shares sequence homology with retrovirus-related reverse transcriptase which is thought to be important in viral replication. One  
30 embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence: TTKENCRRPASLMNIDTKILNKILMNQ (SEQ ID NO:640). An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments. (See Accession No. pirlA25313IGNHUL1).

This gene is expressed primarily in human meningioma.

35 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, retroviral diseases such as AIDS, and possibly certain cancers due to transactivation of latent cell division genes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to retrovirus-related reverse transcriptase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of diseases and maladies associated with retroviral infection since a functional reverse transcriptase (RT) or RT-like molecule is an integral component of the retroviral life cycle.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 117

The translation product of this gene shares sequence homology with an unknown gene from *C. elegans*, as well as weak homolog with mammalian metaxin, a gene contiguous to both thrombospondin 3 and glucocerebrosidase, is known to be required for embryonic development. Preferred polypeptide fragments comprise the following amino acid sequence: MCNLPIKVVCRAEYMSPSGKVPXXHVGNGQ VVSELGPIVQFVKAKGHSLSDGLEEVQKAEMKAYMELVNNMLLTAEYLQWC DEATVGXITHXRYGSPYPWPLXHILAYQKQWEVKRXXKAIGWGKKTLTDQVLE DVDQCCQALSQRLGTQPYFFNKQPTELDALVFGHLYTILTTQLTNDELSEKVKN YSNLLAFCRRI EQHYFEDRGKGRLS (SEQ ID NO:641); MCNLPIKVVCRAE YMSPSGKVPXXHVGNGQVVSELGPIVQFVK (SEQ ID NO:642). Also preferred are polynucleotide fragments encoding these polypeptide fragments (See Accession No. gil1326108).

This gene is expressed primarily in fetal tissues and to a lesser extent in hematopoietic cells and tissues, including spleen, monocytes, and T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer, lymphoproliferative disorders; inflammation; chondrosarcoma, and Gaucher disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification



of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and embryonic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression in embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation or cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and survival of hematopoietic cell lineages. Thus, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 118

The translation product of this gene shares sequence homology with reverse transcriptase which is important in the synthesis of a cDNA chain from an RNA molecule, and is a method whereby the infecting RNA chains of retroviruses are transcribed into their DNA complements. One embodiment for this gene is the polypeptide fragment comprising the following amino acid sequence:  
 MXXXNSHITIFTLNVNGLNAPNERHRLANWIQSQDVCCIQETHLTGRDTHRL  
 KIKGWRKIYQANGKQKK (SEQ ID NO:647). An additional embodiment is the polynucleotide fragments comprising polynucleotides encoding these polypeptide fragments (See Accession No. gi2072964).

This gene is expressed primarily in skin and to a lesser extent in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, hematopoietic disorders; inflammation; disorders of immune surveillance. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermis and/or hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and

wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5       The tissue distribution and homology to reverse transcriptase indicates that polynucleotides and polypeptides corresponding to this gene are useful for cancer therapy. Expression in the skin also indicates that this gene is useful in wound healing and fibrosis. Expression by neutrophils also indicates that this gene product plays a role in inflammation and the control of immune surveillance (i.e. recognition of viral
- 10       pathogens). Reverse transcriptase family members are also useful in the detection and treatment of AIDS.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 119**

- 15       The translation product of this gene shares sequence homology with reverse transcriptase which is important in the synthesis of a cDNA copy of an RNA molecule, and is a method whereby a retrovirus reverse-transcribes its genome into an inheritable DNA copy.

This gene is expressed primarily in the frontal cortex of brain.

- 20       Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders
- 25       of the above tissues or cells, particularly of the CNS and peripheral nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
- 30       the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to reverse transcriptase suggest that this is useful in the treatment of cancer and AIDS. The expression in brain indicates that it plays a role in neurodegenerative disorders and in neural degeneration.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 120**

One embodiment of this gene has homology to a hypothetical protein in *Schizosaccharomyces pombe* (See Accession No. 2281980). Another embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:  
5 IYHLHSWIFFHFKRAFCMCFTTMKVIAHCSKLRKCXNAQISVFCTTLTASYPT  
(SEQ ID NO:651). An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments. This gene maps to chromosome 18, and therefore, may be used as a marker in linkage analysis for chromosome 18.

10 This gene is expressed primarily in adult hypothalamus and to a lesser extent in infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurodegenerative disorders; endocrine function; and vertigo. Similarly,  
15 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS and peripheral nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
20 tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
25 corresponding to this gene are useful for the treatment and diagnosis of neurodegenerative disorders; diagnosis of tumors of a brain or neuronal origin; treatments involving hormonal control of the entire body and of homeostasis, behavioral disorders, such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and  
30 panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo.

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**FEATURES OF PROTEIN ENCODED BY GENE NO: 121**

35 The translation product of this gene shares sequence homology with the human IRLB protein which is thought to be important in binding to a c-myc promoter element and thus regulating its transcription (See Accession No. gil33969). This gene maps to

chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in brain and breast and to a lesser extent in a variety of hematopoietic tissues and cells.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer of the brain and breast; lymphoproliferative disorders; neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these  
10 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, breast, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
15 fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of cancer of the  
20 brain, breast, and hematopoietic system. In addition, it may be useful for the treatment of neurodegenerative disorders, as well as disorders of the hematopoietic system, including defects in immune competency and inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 122**

The translation product of this gene shares sequence homology with an ATP synthase, a key component of the proton channel that is thought to be important in the translocation of protons across the membrane.

30 This gene is expressed primarily in T cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, T cell lymphoma. Similarly, polypeptides and antibodies directed to these  
35 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or

lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to ATP synthase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of defects in proton transport, homeostasis, and metabolism, as well as the diagnosis and treatment of lymphoma. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 123**

This gene maps to chromosome 15, and therefore, may be used as a marker in linkage analysis for chromosome 15.

This gene is expressed primarily in a variety of fetal tissues, including fetal liver, lung, and spleen, and to a lesser extent in a variety of blood cells, including eosinophils and T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer (abnormal cell proliferation); T cell lymphomas; and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetus and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions involving cell proliferation. Expression of this gene in fetal tissues, as well as in a variety of blood cell lineages indicates that it may play a role in either cellular proliferation; apoptosis; or cell survival. Thus it may be useful in the management and

treatment of a variety of cancers and malignancies. In addition, its expression in blood cells suggest that it may play additional roles in hematopoietic disorders and conditions, and could be useful in treating diseases involving autoimmunity, immune modulation, immune surveillance, and inflammation..

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 124**

This gene is expressed primarily in placenta and to a lesser extent in pineal gland and rhabdomyosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental, endocrine, and female reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For  
15 a number of disorders of the above tissues or cells, particularly of the [insert system where a related disease state is likely, e.g., immune], expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
20 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 357 as residues: Leu-69 to Val-76.

The tissue distribution indicates that polynucleotides and polypeptides  
25 corresponding to this gene are useful for diagnosis and treatment of disorders in development. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

#### **30 FEATURES OF PROTEIN ENCODED BY GENE NO: 125**

This gene is expressed primarily in benign prostatic hyperplasia.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of benign prostatic hyperplasia. Similarly,  
35 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive

system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of benign prostatic hyperplasia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 126**

This gene is expressed primarily in apoptotic T-cells and to a lesser extent in suppressor T cells and ulcerative colitis.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases involving premature apoptosis, and immunological and gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders involving inappropriate levels of apoptosis, especially in immune cell lineages. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases (such as AIDS), and leukemia.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 127**

This gene is expressed primarily in Raji cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation and T cell autoimmune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 360 as residues: Asp-23 to Gly-29.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of inflammation and T cell autoimmune disorders. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases (such as AIDS), and leukemia.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 128**

The translation product of this gene shares sequence homology with an *C. elegans* coding region C47D12.2 of unknown function (See Accession No. gnllPIDe348986). One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence: EDDGFNRSIHEVILKNITWY  
SERVLTEISLGSLLLLVVIRTIQYNMTRTRDKYLHTNCLAALANMSAQFRSLHQY  
AAQRIISLFSLLSKKHNVLEQATQSLRGSLSNDVPLPDYAQDLNVIEEVIRMM  
LEIINSCLTNSLHHNPVLVALLYKRDLFEQFRTHPSFQDIMQNIDLVISFFSRL  
LQAGS (SEQ ID NO:657); EDDGFNRSIHEVILKNITWYSERVLTEISLGSLLLLV  
(SEQ ID NO:658); RTIQYNMTRTRDKYLHTNCLAALANMSAQFRSLHQYAAQ  
RIISLFSLLSKKHNVLEQATQSLRGSLSNDVPLPDY  
AQD (SEQ ID NO:661); SCLTNSLHHNPVLVALLYKRDLFEQFRTHPSFQ  
IMQNIDLVISFFSRLQAGS (SEQ ID NO:660). An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments. This gene maps to



chromosome 18, and therefore, may be used as a marker in linkage analysis for chromosome 18.

This gene is expressed primarily in smooth muscle and to a lesser extent in fetal liver.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, atherosclerosis and other cardiovascular and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample  
15 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of circulatory system  
20 disorders such as atherosclerosis, hypertension, and thrombosis. In addition, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the  
25 expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 129

30 The translation product of this gene shares sequence homology with a ribosomal protein which is thought to be important in cellular metabolism, in addition to the *C.elegans* protein F40F11.1 which does not have a known function at the current time (See Accession No. gnlIPIDle244552). Preferred polypeptide fragments comprise the following amino acid sequence:

35 MADIQTERAYQKQPTIFQNKKRVLGETGKEKLPRVTNKNIGLGFKDT  
PRLLRGTYIDKKCPFTGNVSIRGRILSGVVTQDEDAEDHCHPPRLSALHPQVQ  
PLREAPQEHVCTPVPL LQGRPDR (SEQ ID NO:662); MKMQRTIVIRRDYLH

YIRKYNRFEKRHKNMSVHLSPCFRDVQIGDIVTVGECRPLSKTVRFNVLKVTK  
 AAGTKKQFQKF (SEQ ID NO:663); MADIQTERAYQKQPTIFQNKKRVLGET  
 GK (SEQ ID NO:664); HCHPPRLSALHPQVQPLREAPQEHVCTPVPL LQGRPDR  
 (SEQ ID NO:666); NIGLGFKDTPRRLRGTYIDKKCPFTGNVSIRGRILSGVVTQ  
 5 (SEQ ID NO:669); MKMQRTTIVIRRDYLHYIRKYNRFEKRHKNMSVHLSP (SEQ  
 ID NO:667); CFRDVQIGDIVTVGECRPLSKTVRFNVLKVTKAAGTKKQFQKF  
 (SEQ ID NO:668). Also preferred are polynucleotide fragments encoding these  
 polypeptide fragments.

10 This gene is expressed primarily in Wilm's tumor and to a lesser extent in  
 thymus and stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, diseases affecting RNA translation. Similarly, polypeptides and  
 15 antibodies directed to these polypeptides are useful in providing immunological probes  
 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 of the above tissues or cells, particularly of the Wilm's tumors, expression of this gene  
 at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial  
 20 fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
 such a disorder, relative to the standard gene expression level, i.e., the expression level  
 in healthy tissue or bodily fluid from an individual not having the disorder. Preferred  
 epitopes include those comprising a sequence shown in SEQ ID NO: 362 as residues:  
 Thr-11 to Asp-20.

25 The tissue distribution and homology to a ribosomal protein indicates that  
 polynucleotides and polypeptides corresponding to this gene are useful for diseases  
 affecting RNA translation.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 130

30 The translation product of this gene shares sequence homology with a yeast  
 DNA helicase which is thought to be important in global transcriptional regulation (See  
 Accession No. gnllPIDe243594). One embodiment for this gene is the polypeptide  
 fragments comprising the following amino acid sequence: IFYDSDWNPTVDQQA  
 MDRAHRLGQTKQVTYRLLICKGTIEERILQRAKEKSEIQRMVISG (SEQ ID  
 35 NO:670); TRMIDLLEEYMVYRKHTYXRLDGSSKISERRDMVADFQNRNDI  
 FVFLSTRAGGLGINLTAXDTVHF (SEQ ID NO:671); TRMIDLLEEYMVYRK  
 HTYXRLDGSSKISERRDM (SEQ ID NO:674); RRDMVADFQNRNDIFVFL

STRAGGLGINLTAXDTVHF (SEQ ID NO:675) , IFYDSDWNPTVDQQAMD  
RAHRLGQTKQVTVYRLICKG (SEQ ID NO:676); RLICKGTIEERILQRAK  
EKSEIQRMVISG (SEQ ID NO:678). An additional embodiment is the polynucleotide  
fragments encoding these polypeptide fragments.

5 This gene is expressed primarily in amygdala.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, diseases and disorders of the brain. Similarly, polypeptides and  
10 antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the central nervous system, expression of  
this gene at significantly higher or lower levels may be routinely detected in certain  
tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,  
15 urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

The tissue distribution and homology to a DNA helicase indicates that  
20 polynucleotides and polypeptides corresponding to this gene are useful for diseases  
affecting RNA transcription, particularly developmental disorders and healing wounds  
since the later are though to approximate developmental transcriptional regulation.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 131**

25 This gene is expressed primarily in prostate and to a lesser extent in amygdala  
and pancreatic tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
30 not limited to, prostate enlargement and gastrointestinal disorders, particularly of the  
pancreas and gall bladder. Similarly, polypeptides and antibodies directed to these  
polypeptides are useful in providing immunological probes for differential identification  
of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
particularly of the reproductive system, expression of this gene at significantly higher or  
35 lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or  
another tissue or cell sample taken from an individual having such a disorder, relative to

the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of prostate diseases, including benign prostatic hyperplasia and prostate cancer. In addition, the tissue distribution in tumors of the pancreas indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tissues where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 132**

This gene is expressed primarily in adult lung and to a lesser extent in hypothalamus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, pulmonary diseases and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of pulmonary and respiratory disorders such as emphysema, pneumonia, and pulmonary edema and emboli. In addition, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental

disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 133**

5        This gene is expressed primarily in human liver.

         Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cirrhosis of the liver and other hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

         The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of liver disorders such as cirrhosis, jaundice, and Hepatitis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

#### **25    FEATURES OF PROTEIN ENCODED BY GENE NO: 134**

         This gene is expressed primarily in fetal kidney and to a lesser extent in fetal liver and spleen.

         Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, development and regeneration of liver and kidney and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and excretory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 367 as residues: Pro-70 to Arg-77, Tyr-102 to Thr-107.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the kidney and liver, such as cirrhosis, kidney failure, kidney stones, and liver failure, hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 135**

This gene is expressed primarily in brain, bone marrow, and to a lesser extent in placenta, T cell, testis and neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurodegenerative and immunological diseases and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 368 as residues: Met-1 to His-6.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also

play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

# FEATURES OF PROTEIN ENCODED BY GENE NO: 136

- 5 Translation product of this gene is homologous to the human WD repeat protein HAN11. Preferred polypeptide fragments comprise the following amino acid sequence:
- MSLHGKRKEIYKYEAPWTVYAMNWSVRPDKRFRLLALGSFVEEYNNKVQLVG  
LDEESSEFICRNTFDHPYPTTKLMWIPDTKGVYPDLLATSGDYLRVWRVGETET  
10 RLECLLNNNKNSDFCAPLTSFDWNEVDPYLLGTSSIDTTCTIWGLETGQVLGRV  
NLVSGHVKTQLIAHDKEYDIAFSRAGGGRDMFASVGADGSVRMFDLRHLEH  
STIYEDPQHHPDLLRLCWNKQDPNYLATMAMDGMEVVILDVRVPAHLXPGTTIE  
HVSMAILGPHIHPATSALQRM TTRLSSGTSSKCPEPLRTL SWPTQLXGEINNVQ  
WASTQPELSPSATTAWRYSECSVGGA VPTRQGLLYFLPLPHPQS (SEQ ID  
15 NO:679); MSLHGKRKEIYKYEAPWTVYAMNWSVRPDKRFRLLALGSFV  
EEYNNKVQLVGLDEESSEFICRNTFDHPYPTTKLMWIPDTKGVYPDLLATSGDY  
LRVWRVGETETRLECLLNNNKNSDFCAPLTSFDWNEVDPYLL (SEQ ID  
NO:680); SFDWNEVDPYLLGTSSIDTTCTIWGLETGQVLGRVNLVSGHVK  
TQLIAHDKEYDIAFSRAGGGRDMFASVGADGSVRMFDLRHLEHSTIYEDPQH  
20 HPLLRLCWNKQDPNYLATMAMDGMEVVILDVRVPAHLXPGTTI (SEQ ID  
NO:681); VGADGSVRMFDLRHLEHSTIYEDPQHHPDLLRLCWNKQDPNYLA  
TMAMDGMEVVILDVRVPAHLXPGTTIEHVSMAILGPHIHPATSALQRM TTRL  
SGTSSKCPEPLRTL SWPTQLXGEINNVQWASTQPELSPSATTAWRYSECSVG  
GAVPTRQGLLYFLPLPHPQS (SEQ ID NO:682). Also preferred are polynucleotide  
25 fragments encoding these polypeptide fragments.

This gene is expressed primarily in placenta, embryo, T cell and fetal lung and to a lesser extent in endothelial, tonsil and bone marrow.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunological and developmental diseases in addition to cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
35 immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or

cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 369 as residues: Gly-19 to Gln-28, Pro-36 to Phe-42.

- 5       The tissue distribution in tumors of colon, ovary, and breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above
- 10   listed tumors and tissues. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

15   **FEATURES OF PROTEIN ENCODED BY GENE NO: 137**

This gene is expressed primarily in TNF and INF induced epithelial cells, T cells and kidney.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a
- 20   biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammatory conditions particularly inflammatory reactions in the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of renal
- 25   system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an
- 30   individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 370 as residues: Thr-67 to Gly-72, Gln-132 to Ala-145, Arg-150 to Pro-157.

The tissue distribution indicates that the protein products of this gene are useful for treating the damage caused by inflammation of the kidney.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 138**

This gene maps to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1 (See Accession No. D63485).

5 This gene is expressed primarily in breast cancer and colon cancer and to a lesser extent in thymus and fetal spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancers, especially of the breast and colon tissues. Similarly,  
10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum,  
15 plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of colon and breast origins indicates that  
20 polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

**25 FEATURES OF PROTEIN ENCODED BY GENE NO: 139**

This gene maps to chromosome 17, and therefore, can be used as a marker for linkage analysis from chromosome 17.

This gene is expressed primarily in CD34 positive cells, and to lesser extent in activated T-cells and neutrophils.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunologically related diseases and hematopoietic disorders. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
35 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and hematopoietic system, expression of this gene at significantly higher or lower levels

may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in CD34, T-cell and neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of hematopoietic disorders and immunologically related diseases, such as anemia, leukemia, inflammation, infection, allergy, immunodeficiency disorders, arthritis, asthma, immune deficiency diseases such as AIDS.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 140

This gene was recently cloned by another group, who called the gene KIAA0313 gene. (See Accession No. d1021609.) Preferred polypeptide fragments comprise the amino acid sequence:

LYATATVISSPSTEXLSQDQGDRASLDAADSGRGSWTSCSSGSHDNIQTIQ  
HQRSWETLPGFHTHFDYSGDPAGLWASSSHMDQIMFSDHSTKYNRQNSRES  
LEQAQSRASWASSTGYWGEDSEGDGTIKRRGGKDV SIEAESSSLTSVTTEETK  
PVPMPAHIAVASSTTKGLIARKEGRYREPPPTPPGYIGIPITDFPEGHSH PARKP  
PDYNVALQSRMRVARSSDTAGPSSVQQPHGHPTSSRPVNKPQWHKXNESDP  
LAPYQSQGFSTEEDEDEQVSAV (SEQ ID NO:683); HMDQIMFSDHSTKYNRQ  
NQSRESLEQAQSRASWASSTGYWGE (SEQ ID NO:684); SVTTEETKPVPMP  
AHIAVASSTTKGLIARKEGRYREPPPTPPGYIGIPITD (SEQ ID NO:685); and  
VALQSRMRVARSSDTAGPSSVQQPHGHPTSSRPVNKPQW

HKXNESDPRLAPYQSQGF (SEQ ID NO:686). Also preferred are polynucleotide fragments encoding these polypeptide fragments. This gene maps to chromosome 4, and therefore, may be used as a marker in linkage analysis for chromosome 4 (See Accession No. AB002311).

This gene is expressed primarily in ovarian cancer, tumors of the Testis, brain, and colon.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, ovarian, testicle, brain and colon cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male and female reproductive systems,

expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of colon, ovary, testis, and brain origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 141**

This gene is expressed primarily in spleen and colon cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, colon cancer and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal tract and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of colon, ovary, and breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 142**

Translation product is homologous to T cell translocation protein, a putative zinc finger factor (See Accession No. 340454), as well as to the G-protein coupled receptor TM5 consensus polypeptide (See Accession No. R50734). Preferred polypeptide fragments comprise the following amino acid sequence:

CLLFV FVSLGM RCLFW TTVYN VLYLK HKCNT VLLCY HLC SI (SEQ ID NO:687);  
ACSKL IPAFEM VMRAK DNVYH LDCFAC QLCNQR XC VGDKFF LKNNXX LCQT  
DYEEGL MKEGY APXVR (SEQ ID NO:688). Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neurological disorders including brain cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Central Nervous System, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 143**

Translation product for this gene has significant homology to the Fas ligand, which is a cysteine-rich type II transmembrane protein/tumor necrosis factor receptor homolog. Mutations within this protein have been shown to result in generalized lymphoproliferative disease leading to the development of lymphadenopathy and autoimmune disease (See Medline Article No. 94185175). Preferred polypeptide

fragments comprise the following amino acid sequence:

SALSEPGAPDRRRPCPESVPRRPDDEQWPPPTALCLDVAPLPPSS (SEQ ID NO:669). Also preferred are polynucleotide fragments encoding these polypeptide fragments (See Accession No. 473565).

5 This gene is expressed primarily in osteoblasts, lung, and brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, osteoblast-related, pulmonary, neurological, and immunological  
10 diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
15 tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 376 as residues: Trp-33 to Thr-40, Lys-  
20 45 to Ile-63.

The tissue distribution in osteoblasts, lung, and brain combined with its homology to the Fas ligand indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as,  
25 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Because the Fas ligand gene is known to be expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including asthma, immune deficiency diseases such as AIDS  
30 and leukemia, and various autoimmune disorders including lupus and arthritis.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 144

This gene shares sequence homology with a 21.5 KD transmembrane protein in the SEC15-SAP4 intergenic region of yeast. (See Accession No. 1723971.) Preferred  
35 polypeptide fragments comprise the amino acid sequence:  
AHASESGERWWACCGVRFGLRSIEAIGRSCCHDGPGLVANRGRRFKWAIEL  
SGPGGGSRGRSDRGSQGDSLYPVGYLDKQVPDTSVQETDRILVEKRCWDIAL

GPLKQIPMNLFI MYMAGNTISIFPTMMVCMMAWRPIQALMAISATFKMLESSSQ  
 KFLQGLVYLIGNLMGLALAVYKCQSMGLLPTHASDWLAFIEPPERMEFSGG  
 GLLL (SEQ ID NO:691); PVGYLDKQVPDTSVQETDRILVEKRCWDIALGPLKQ  
 IPMNLFI (SEQ ID NO:693); and ATFKMLESSSQKFLQGLVYLIGNLMGLALAV  
 5 YKCQSMGLLPTHASD (SEQ ID NO:692). Also preferred are polynucleotide  
 fragments encoding these polypeptide fragments.

This gene is expressed primarily in osteoclastoma, hemangiopericytoma, liver,  
 lung.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 10 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, osteoclastoma, hemangiopericytoma, liver and lung tumors. Similarly,  
 polypeptides and antibodies directed to these polypeptides are useful in providing  
 immunological probes for differential identification of the above tissue(s) or cell  
 15 type(s). For a number of disorders of the above tissues or cells, particularly of the lung  
 and liver systems, expression of this gene at significantly higher or lower levels may be  
 routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily  
 fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or  
 cell sample taken from an individual having such a disorder, relative to the standard  
 20 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
 corresponding to this gene are useful for diagnosing osteoclastoma,  
 hemangiopericytoma, liver and lung tumors.

## 25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 145**

Translation product of this gene shares homology with the glucagon-69 gene  
 which may indicate this gene plays a role in regulating metabolism. (See Accession No.  
 A60318) One embodiment for this gene is the polypeptide fragments comprising the  
 30 following amino acid sequence:  
 PTTKLDIMEKKKKHIQIRFSPFYHKLVDSGRMRSKRETRREDSDTKHNL (SEQ ID  
 NO:694). An additional embodiment is the polynucleotide fragments encoding these  
 polypeptide fragments.

This gene is expressed primarily in brain, kidney, colon, and testis.

35 Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, brain, kidney, colon, and testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, neurological, circulatory, and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of brain, kidney, colon, and testis origins, indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

## 25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 146**

The translation product of this gene shares sequence homology with goliath protein which is thought to be important in the regulation of gene expression during development. Protein may serve as a transcription factor. One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:

30 TEHIIA VMITELRGKDILSYLEKNISVQMTIAVGTRMP PKNFSRGS LVFVSISFIV  
LMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKKGDKETD  
PDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCPMCKLNILKA  
LGIV (SEQ ID NO:695); TEHIIA VMITELRGKDILSYLEKNISVQMTIAVGTRMP  
PKNFSRGS LVFVSISFIVLM IISSAWLIFYF (SEQ ID NO:697); SISFIVLMISSA  
35 WLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTVKKGDKE (SEQ ID  
NO:698); VKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDP

WLSEHCTCPMCKLNILKALGIV (SEQ ID NO:699). An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments (See Accession No. 157535). Moreover, another embodiment is the polynucleotide fragments encoding these polypeptide fragments:

- 5 MTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTIA VGTRMPPKNFSRGS  
LVFVSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRR LGDAAKKAISKLTTRTV  
KKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCP  
MCKLNILKALGIVPNLPCTDNVAFDMERLTRTQAVNRRSALGDLAGDNSLGL  
PLRTSGISPLPQDGELTPRTGEINIA VTKEWFIIASFGLLSALTLCYMIIRATASLN  
10 ANEVEWF (SEQ ID NO:696); MTHPGTEHIIA VMITELRGKDILSYLEKNISVQMTIA  
VGTRMPPKNFSRGS LVFVSISFIVLMISSAWLIFYFIQKIRYTNARDRNQRR  
LGDAAKKAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRILPCKHVFHKSCVDPWLSEHCTCPMCKLNIL  
KALGIVPNLPC (SEQ ID NO:701); TQAVNRRSALGDLAGDNSLGLPLRTSGI  
15 SPLPQDGELTPRTGEINIA VTKEWFIIASFGLLSALTLCYMIIRATASLNANEVEW  
F (SEQ ID NO:702); PLHGVADHLGCDPQTRFFVPPNIKQWIALLRGNCTF  
KEKISRAAFHNAVAVVIYNNKSKEEPTMTHTPGTEHIIA VMITELRGKDILSYLE  
KNISVQMTIA VGTRMPPKNFSRGS LVFVSISFIVLMISSAWLIFYFIQKIRYTN  
ARDRNQRR LGDAAKKAISKLTTRTVKKGDKETDPDFDHCAVCIESYKQNDVVRIL  
20 LPCKHVFHKSCVDPWLSEHCTCPMCKLNILKALGIVPNLPCTDNVAFDMERLT  
RTQAVNRRSALGDLAGDNSLGLPLRTSGISPLPQDGELTPRTGEINIA VTKEW  
FIASFGLLSALTLCYMIIRATASLNANEVEWF (SEQ ID NO:703); and  
HGVADHLGCDPQTRFFVPPNIKQWIALLRGNCTFKEKISRAAFHNAVAVVIY  
NNKSKEE (SEQ ID NO:704). An additional embodiment is the polynucleotide  
25 fragments encoding these polypeptide fragments. When tested against Jurkat cell lines,  
supernatants removed from cells containing this gene activated the GAS pathway.  
Thus, it is likely that this gene activates immune cells through the JAKS/STAT signal  
transduction pathway.

- 30 This gene is expressed primarily in macrophage, breast, kidney and to a lesser  
extent in synovium, hypothalamus and rhabdomyosarcoma.

- Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, schizophrenia and cancer. Similarly, polypeptides and antibodies directed  
35 to these polypeptides are useful in providing immunological probes for differential  
identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the immune and neural system, expression of this gene at



significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to zinc finger protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of schizophrenia, kidney disease and other cancers. The tissue distribution in macrophage, breast, and kidney origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors within these tissues, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 147

The translation product of this gene shares sequence homology with HNP36 protein, an equilibrative nucleoside transporter, which is thought to be important in gene transcription as well as serving as an important component of the nucleoside transport apparatus (See Accession No. 1845345). One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:

MSGQGLAGFFASVAMICAIASGSELSAFAFGYFITACAVIILTICYLGLPRLEFYR  
 YYQQLKLEGPGEQETKLDLISKGEEPRAGKEESGVSVSNSQPTNESHSHKAILK  
 NISVLAFSVCFITTTIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLT FNIFDWLG  
 RSLTAVFMWPGKDSRWLPSWXLARLVFVPLLLCNKPRRYLTVVFEHDAWFI  
 FFMAAFASNGYLASLCMCFGPKKVKPAEAETAEPSPSSCVVWHWGLFS  
 PSCSGQLCDKGWTEGLPASLPVCLLPARGDPEWSGGFFF (SEQ ID  
 NO:705); MSGQGLAGFFASVAMICAIASGSELSAFAFGYFITACAVIILTIC  
 YLGLPRLEFYRYYYQQLKLE GPGEQETKLDLISKGEEPRAGKEESGVSVSNSQ  
 PTNESHSH (SEQ ID NO:706); SGVSVSNSQPTNESHSHKAILKNISVLAFSVCFI  
 FTTTIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLT FNIFDWLGRS (SEQ ID  
 NO:707); TIGMFPAVTVEVKSSIAGSSTWERYFIPVSCFLT FNIFDWLGRSLTAVF  
 MWPGKDSRWLPSWXLARLVFVPLLLCNKPRRYLTVVFEHDA (SEQ ID  
 NO:708); FGPKKVKPAEAETAEPSPSSCVVWHWGLFSPSCSGQLCDK

GWTEGLPASLPVCLLPSPARGDPEWSSGGFFF (SEQ ID NO:709). An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in eosinophils and aortic endothelium and to a lesser extent in umbilical vein endothelial cell and thymus.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematopoietic disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
10 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
15 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to HNP36 protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of blood neoplasias and other hematopoietic disease.

#### 20 **FEATURES OF PROTEIN ENCODED BY GENE NO: 148**

This gene is expressed primarily in breast cancer cell lines, thymus stromal cells, and ovary.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, endocrine and female reproductive system diseases including breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
30 type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard  
35 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of endocrine disorders. In addition, the tissue distribution in tumors of thymus, ovary, and breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues

#### 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 149

Translation product of this gene has homology to pmt1 and pmt 2, two conserved schizosaccharomyces pombe genes. One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:  
 DDDGFEIVPIEDPAKHRILDPEGLALGAVIASSKKAKRDLIDNSFNRYTFNEDEG  
 15 ELPEWFVQEEKQHRIRQLPVGKKEVEHYRKRWREINARPIXXXXXXXXXXXXX  
 XXXXXXLEQTRKKAEEVVNTVDIXRTRES (SEQ ID NO:710);  
 DDDGFEIVPIEDPAKHRILDPEGLALGAVIASSKKAKRDLIDNSFNRYTF (SEQ  
 ID NO:711); KRWREINARPIXXXXXXXXXXXXXXXXXXXXLEQTRKKAEE  
 AVVNTVDIXRTRES (SEQ ID NO:712). An additional embodiment is the  
 20 polynucleotide fragments encoding these polypeptide fragments (See Accession No.  
 e1216734).

This gene is expressed primarily in retina and ovary and to a lesser extent in breast cancer cell, epididymus and osteosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 25 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, neuronal growth disorders, cancer and reproductive system disorders.  
 Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
 providing immunological probes for differential identification of the tissue(s) or cell  
 30 type(s). For a number of disorders of the above tissues or cells, particularly of the  
 neural and reproductive system, expression of this gene at significantly higher or lower  
 levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
 tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or  
 another tissue or cell sample taken from an individual having such a disorder, relative to  
 35 the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 fluid from an individual not having the disorder. Preferred epitopes include those  
 comprising a sequence shown in SEQ ID NO: 382 as residues: Met-1 to Gly-7.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or treatment of reproductive system disease and cancers.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 150

One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:

MIKDKGRARTALTSSQPAHLCPENPLLHLKAAVKEKKRNKKKKTIGSPKRIQS  
 PLNNKLLNSPAKTLPGACGSPQKLIDGFLKHEGPPAEKPLEELSASTSGVPGLS  
 10 SLQSDPAGCVRPPAPNLAGAVEFNDVKTLREWITTISDPMEEDILQVVKYCTD  
 LIEEKDLEKLDLVIKYMKRLMQQSVEVWNMAFDLQVQVVLQQTGYSTLK  
 VT (SEQ ID NO:713); MIKDKGRARTALTSSQPAHLCPENPLLHLKAAVKE  
 KKRNNKKKTIGSPKRIQ (SEQ ID NO:714); KRIQSPLNNKLLNSPAKT  
 LPGACGSPQKLIDGFLKHEGPPAEKPLEELSASTSGVPGLSSLQSDPAGCVRPP  
 15 APNLAGAVEFNDVKTLREWITTISDPM (SEQ ID NO:715);  
 TISDPMEEDILQVVKYCTDLIEEKDLEKLDLVIKYMKRLMQQSVE  
 SVWNMAFDLQVQVVLQQTGYSTLKVT (SEQ ID NO:716). An additional  
 embodiment is the polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in 12 week embryo and to a lesser extent in  
 20 hemangiopericytoma and frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, growth disorders and hemangiopericytoma. Similarly, polypeptides and  
 25 antibodies directed to these polypeptides are useful in providing immunological probes  
 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 of the above tissues or cells, particularly of the circular and neural system, expression  
 of this gene at significantly higher or lower levels may be routinely detected in certain  
 tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,  
 30 urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an  
 individual having such a disorder, relative to the standard gene expression level, i.e.,  
 the expression level in healthy tissue or bodily fluid from an individual not having the  
 disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO: 383 as residues: Leu-4 to Lys-11.

35 The tissue distribution indicates that polynucleotides and polypeptides  
 corresponding to this gene are useful for the treatment of growth disorders,  
 hemangiopericytoma and other soft tissue tumors.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 151**

The translation product of this gene has been found to have homology to a human DNA mismatch repair protein PMS3. Preferred polypeptide fragments comprise the following amino acid sequence: FCHDCKFPEASPAMNCEP (SEQ ID NO:717). Also preferred are polynucleotide fragments encoding these polypeptide fragments (See Accession No. R95250).

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, lymphoma, immunodeficiency diseases, and cancers resulting from genetic instability. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 384 as residues: Met-1 to Lys-6.

The tissue distribution in neutrophils and the sequence homology indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis of Hodgkin's lymphoma, since the elevated expression and secretion by the tumor mass may be indicative of tumors of this type. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Furthermore, its homology to a known DNA repair protein would suggest gene may be useful in establishing cancer predisposition and prevention in gene therapy applications.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 152**

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, infectious diseases and lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of inflammation and infectious diseases.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 153**

One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence:

MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKC

NFFCWDSSAHSPLHPLSASCSAPACHASDTHLLYPSTRALCPSIFAWLVAPHS

20 VFRTNAPGPTPSSQSSPVFPVFPVSFMALIVCXLVCC (SEQ ID NO:720);

MASSVPAGGHTRAGGIFLIGKLDLEASLFKSFQWLPFVLRKKCNFFCWDSSAH

SLPLHPLSASCSAPACHA (SEQ ID NO:721);FAWLVAPHSVFRTNAPGPTPS

SQSSPVFPVFPVSFMALIVCXLVCC (SEQ ID NO:722). An additional embodiment is the polynucleotide fragments encoding these polypeptide fragments.

25 This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammation and infectious disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred

epitopes include those comprising a sequence shown in SEQ ID NO: 386 as residues: Ser-11 to Pro-17.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of infectious diseases and inflammation.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 154**

This gene is expressed in multiple tissues including ovary, uterus, adipose tissue, brain, and the liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, uterine, ovarian, brain, and liver cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnostic or therapeutic uses in the treatment of the female reproductive system, obesity, and liver disorders, particularly cancer in the above tissues.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 155**

This gene maps to chromosome 3, and therefore, may be used as a marker in linkage analysis for chromosome 3 (See Accession No. D87452).

This gene is expressed in multiple tissues including brain, aortic endothelial cells, smooth muscle, pituitary, testis, melanocytes, spleen, neutrophils, and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunological disorders including immunodeficiencies, cancers of the brain and the female reproductive system, as well as cardiovascular disorders, such as

atherosclerosis and stroke. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at

5 significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 The tissue distribution suggest that polynucleotides and polypeptides corresponding to this gene are useful in treatment/detection of disorders in the nervous system, including schizophrenia, neurodegeneration, neoplasia, brain cancer as well as cardiovascular and female reproductive disorders including cancer within the above tissues.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 156**

The translation product of this gene shares sequence homology with the human gene encoding cytochrome b561 (See Accession No. P10897). Cytochrome b561 is a transmembrane electron transport protein that is specific to a subset of secretory vesicles

20 containing catecholamines and amidated peptides. This protein is thought to supply reducing equivalents to the intravesicular enzymes dopamine-beta-hydroxylase and alpha-peptide amidase. Preferred polypeptides of the invention comprise the amino acid sequence:

MAMEGYWRFLALLGSALLVGFLSVIFALVWVLHYREGLGWDGSALEFNWHP  
 25 VLMVTGFVFIQGIIVYRLPWTWKCSKLLMKSIHAGLNAVAAILAISVVAVFE  
 NHNVNNIANMYSLHSWVGLIAVICYLLQLLSGFSVFLLPWAPLSLRAFLMPIHV  
 YSGIVIFGTVIATALMGLTEKLIFSLRDPAYSTFPPEGVFVNTLGLLLLVFGALIF  
 WIVTRPQWKRPKEPNSTILHPNGGTEQGARGSMPAYSGNNMDKSDSEL  
 NSEVAARKRNLALDEAGQRSTM (SEQ ID NO:724); as well as antigenic fragments

30 of at least 20 amino acids of this gene and/or biologically active fragments. Also preferred are polynucleotide fragments encoding these polypeptide fragments.

This gene is expressed primarily in anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as

35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune system and metabolism related diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological



probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, 5 urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein product or RNA of this gene is 10 useful for treatment or diagnosis of immune system and metabolic diseases or conditions including Tay-Sachs disease, phenylketonuria, galactosemia, various porphyrias, and Hurler's syndrome.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 157**

15 The translation product of this gene shares sequence homology with collagen which is important in mammalian development. This gene also shows sequence homology with bcl-2. (See Accession No. P80988.) Preferred polypeptide fragments comprise the amino acid sequence: PGRAGPSPGLSLQLPAEPGHPAGNLAPL 20 TSRPQPLCRIPAVPG (SEQ ID NO:725). Also preferred are polynucleotide sequences encoding this polypeptide fragment.

This gene is expressed primarily in HL-60 tissue culture cells and to a lesser extent in liver, breast, and uterus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a 25 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunological diseases, hereditary disorders involving the MHC class of immune molecules, as well as developmental disorders and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell 30 type(s). For a number of disorders of the above tissues or cells, particularly of the immune and reproductive system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to 35 the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those

comprising a sequence shown in SEQ ID NO: 390 as residues: Ser-39 to Gly-46, Leu-49 to Ala-62.

5 The tissue distribution and homology to collagen indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of hereditary MHC disorders and particularly autoimmune disorders including rheumatoid arthritis, lupus, scleroderma, and dermatomyositis, as well as many reproductive disorders, including cancer of the uterus, and breast tissues.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 158**

10 This gene is expressed primarily in the amygdala region of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, a variety of brain disorders, particularly those effecting mood and personality. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and/or diagnosis of a variety of brain disorders, particularly bipolar disorder, unipolar depression, and dementia.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 159**

30 This gene is expressed in a variety of tissues and cell types including brain, smooth muscle, kidney, salivary gland and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancers of a variety of organs including brain, smooth muscle, kidney, salivary gland and T-cells and cardiovascular disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders

of the above tissues or cells, particularly of the central nervous, urinary, salivary, digestive, and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain, smooth muscle, and T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis of various neurological, and cardiovascular disorders, but not limited to cancer within the above tissues. Additionally the gene product may be used as a target in the immunotherapy of the cancer. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 160**

The translation product of this gene shares sequence homology with collagen which is thought to be important in cellular interactions, extracellular matrix formation, and has been found to be an identifying determinant in autoimmune disorders. Moreover, this gene shows sequence homology with the yeast protein, Sls1p, an endoplasmic reticulum component, involved in the protein translocation process in Yeast *Yarrowia lipolytica*. (See Accession No. 1052828; see also J. Biol. Chem. 271, 11668-11675 (1996).) With mouse, this same region shows sequence homology with the heavy chain of kinesin. (See Accession No. 2062607.) Recently, suppression of the heavy chain of kinesin was shown to inhibit insulin secretion from primary cultures of mouse beta-cells. (See Endocrinology 138 (5), 1979-1987 (1997).) Moreover, kinesin was found associated with drug resistance and cell immortalization. (See 468355.) Thus, it is likely that this gene also act as a genetic suppressor elements.

This gene is expressed primarily in the greater omentum and to a lesser extent in a variety of organs and cell types including gall bladder, stromal bone marrow cells, lymph node, liver, testes, pituitary, and thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders of the endocrine, gastrointestinal, and immunological systems, including autoimmune disorders and cancers in a variety of organs and cell types.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and gastrointestinal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 393 as residues: Asn-27 to Leu-47, Gln-81 to Lys-88, Asp-93 to Lys-102, Asn-107 to Leu-116, Met-129 to Glu-141, Glu-150 to Asp-157, Lys-176 to Glu-185, Glu-333 to Tyr-349, Cys-393 to Leu-403, Gln-423 to Gly-429.

The tissue distribution in within various endocrine and immunological tissues combined with the sequence homology to a conserved collagen motif indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis of various autoimmune disorders including, but not limited to, rheumatoid arthritis, lupus erythematosus, scleroderma, dermatomyositis. Because the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 161**

This gene has homology to the tissue inhibitor of metalloproteinase 2. Such inhibitors are vital to proper regulation of metalloproteins such as collagenases (See Accession No. P16368). In addition, this gene maps to chromosome 17, and therefore, may be used as a marker in linkage analysis for chromosome 17 (See Accession No. P16368).

This gene is expressed primarily in several types of cancer including osteoclastoma, chondrosarcoma, and rhabdomyosarcoma and to a lesser extent in several non-malignant tissues including synovium, amygdala, testes, placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, various types of cancer, particularly cancers of bone and cartilage, as well as various autoimmune disorders. Similarly, polypeptides and antibodies directed

to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculoskeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in various cancers and the sequence homology to a collagenase inhibitor indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 162**

This gene is homologous to the mitochondrial ATP6 gene and therefore is likely a homolog of this gene family (See Accession No. X76197).

This gene is expressed primarily in brain tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, a variety of brain disorders, including Down's syndrome, depression, Schizophrenia, and epilepsy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain tissue indicates this gene is useful for diagnosis of various neurological disorders including, but not limited to, brain cancer.

Additionally the gene product may be used as a target in the immunotherapy of cancer in the brain as well as for the diagnosis of metabolic disorders such as obesity Tay-Sachs disease, phenylketonuria and Hurler's Syndrome.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 163**

This gene is expressed primarily in placenta, neutrophils, and microvascular endothelial cells and to a lesser extent in multiple tissues including brain, prostate, spleen, thymus, and bone.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neutropenia and other diseases of the immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in placenta indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis various female reproductive disorders. Additionally the gene product may be used as a target in the immunotherapy of various cancers. Because the gene is expressed in some cells of lymphoid and endocrine origin, the natural gene product may be involved in immune functions and metabolism regulation, respectively. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 164**

This gene is expressed primarily in neutrophils, monocytes, bone marrow, and fetal liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune system disorders including, but not limited to, autoimmune disorders such as lupus, and immunodeficiency disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders

of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having  
 5 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in various immune system tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis of various immunological disorders such as Hodgkin's lymphoma, arthritis,  
 10 asthma, immune deficiency diseases such as AIDS, and leukemia.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 165

The translation product of this gene shares sequence homology with dystrophin which is thought to be defective in both Duchene and Becker Muscular Dystrophy.

15 Preferred polypeptide fragments comprise the following amino acid sequence:

MKLLGECSSSIDSVKRLEHKLKEEEESLPGFVNLHSTETQTAGVIDRWELLQAQ  
 ALSKELRMKQNLQKWQQFNSDLNSIWAWLGDTEEELEQLQRLELSTDIQTIELQ  
 IKKLKELQKAVDHRKAILLSINLCSPEFTQADSKESRDLQDRLXQMNGRWDRV  
 CSLLEEWGRLQDALMQCQGFHEMESHGLLLMLLENIDRRKNEIVPIDSNLDAEIL  
 20 QDHHKQLMQIKHELLESQLRVASLQDMSCQLLVNAEGTDCLEAKEKVVHIGNR  
 LKLLLKEVSRHIKELEKLLDVSSSQDLSSWSSADELDTSGSVSPXSGRSTPNR  
 QKTPRGKCSLSQPGPSVSSPHSRSTKGGSDSSLSEXPGRSGRGFLFRVLRAA  
 LPLQLLLLLLIGLACLVPMSSEEDYSCALSNNFARSFHPMLRYTNGPPPL (SEQ ID  
 NO:726); MKLLGECSSSIDSVKRLEHKLKEEEESLPGFVNLHSTETQTAGVIDR  
 25 WELLQAQALSKELRMKQNLQKWQQFNSDLNSIWAWLGDTEEELEQLQRLELS  
 TDIQTIELQIK (SEQ ID NO:727); KLKELQKAVDHRKAILLSINLCSPEFTQADSK  
 ESRDLQDRLXQMNGRWDRVCSLLEEWGRLQDALMQCQGFHEMESHGLLLML  
 ENIDRRKNEIVPIDSNLDAEILQDHHKQLMQIKHELLESQLRVASLQDMSCQL  
 (SEQ ID NO:728); QDMSCQLLVNAEGTDCLEAKEKVVHIGNRLKLLLKEVS  
 30 RHIKELEKLLDVSSSQDLSSWSSADELDTSGSVSPXSGRSTPNRQKTPRGKCS  
 LSQPGPSVSSPHS (SEQ ID NO:729); DSSLSEXPGRSGRGFLFRVLRAAL  
 PLQLLLLLLIGLACLVPMSSEEDYSCALSNNFARSFHPMLRYTNGPPPL (SEQ ID  
 NO:730). Also preferred are polynucleotide fragments encoding these polypeptide

35 fragments. Furthermore, this gene maps to chromosome 6, and therefore, may be used as a marker in linkage analysis for chromosome 6 (See Accession No. N62896).

This gene is expressed in numerous tissues including the heart, kidney, and brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, musculoskeletal disorders including Muscular Dystrophy and cardiovascular diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscle tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to dystrophin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of Muscular Dystrophy and other muscle disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 166**

This gene is expressed primarily in human cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the central nervous system, including Alzheimer's Disease, Parkinson's Disease, ALS, and mental illnesses. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 399 as residues: Pro-20 to Gly-26, Leu-37 to Pro-42, His-57 to Gly-63.

The tissue distribution indicates that the protein products of this gene are useful for treatment/diagnosis of diseases of the central nervous system and may protect or



enhance survival of neuronal cells by slowing progression of neurodegenerative diseases.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 167**

5 Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

MKLLICGNYLAPSHSESSRRCCLLCFYPLCLEINFGMKVFLSMPFLVLFQ

SLIQED (SEQ ID NO:731). Polynucleotides encoding such polypeptides are also provided. This gene is believed to reside on chromosome 15. Therefore polynucleotides  
10 derived from this gene are useful in linkage analysis as chromosome 15 markers.

This gene is expressed primarily in human testes tumor and to a lesser extent in normal human testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
15 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the testes, particularly cancer, and other reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
20 the male reproductive tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
25 fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for treatment/diagnosis of testicular diseases including cancers.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 168**

30 This gene is expressed primarily in fetal liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, conditions affecting hematopoietic development and metabolic diseases.

35 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the

hepatic system, and fetal hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 401 as residues: His-7 to Trp-17, Leu-19 to Lys-27, Pro-33 to Gly-44, Lys-68 to Gly-74, Lys-85 to Cys-95.

The tissue distribution indicates that the protein products of this gene are useful for treatment/diagnosis of diseases of the developing liver and hematopoietic system, and act as a growth differentiation factor for hematopoietic stem cells.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 169

The polypeptide encoded by this gene is believed to be a membrane bound receptor. The extracellular domain of which is expected to consist of the following amino acid sequence:

RILLVKYSANEENKYDYLPPTVNVCSELVKLVFCVLVSFCVIKKDHQSRNLKY  
ASWKEFSDFMKWSIPAFLYFLDNLIVFYVLSYLQPAMAVIFS NFSIITTALLFRIV  
LKXRLNWIQWASLLTLFLSIVALTAGTKTLQHNLAGRGFHDAFFSPSNSCLL  
FRNECPRKDNCTAKEWTFPEAKWNTTARVFSHIRLGMGHVLIIVQCFISSMANI  
YNEKILKEGNQLTEXIFIQNSKLYFFGILFNGLTLGLQRSNRDQIKNCGFFYGH

S (SEQ ID NO:732). Thus, preferred polypeptides encoded by this gene comprise the extracellular domain as shown above. It will be recognized, however, that deletions of either end of the extracellular domain up to the first cysteine from the N-terminus and the first cysteine of the C-terminus, is expected to retain the biological functions of the full-length extracellular domain because the cysteines are thought to be responsible for providing secondary structure to the molecule. Thus, deletions of one or more amino acids from either end (or both ends) of the extracellular domain are contemplated. Of course, further deletions including the cysteines are also contemplated as useful as such polypeptides is expected to have immunological properties such as the ability to evoke and immune response. Polynucleotides encoding all of the foregoing polypeptides are provided.

This gene is expressed primarily in human osteoclastoma and to a lesser extent in hippocampus and chondrosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, cancers, particularly those of the bone and connective tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 402 as residues: Met-1 to Cys-6, Ala-41 to Tyr-49, Lys-76 to Lys-84.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis of cancers of the bone and connective tissues, and may act as growth factors for cells involved in bone or connective tissue growth.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 170**

Preferred polypeptides encoded by this gene comprising the following amino acid sequence:

NSVPNLQTLAVLTEAIGPEPAIPRXPREPPVATSTPATPSAGPQPLPTGTV

LVPGGPAPPCLGEAWALLLPPCRPSLTSCFWSPRPSPWKETGV (SEQ ID NO:733). Polynucleotides encoding such polypeptides are also provided herein.

This gene is expressed primarily in hematopoietic progenitor cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the blood including cancer and autoimmune disorders.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the blood/circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 403 as residues: Gln-4 to His-10, Pro-25 to His-32.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis of diseases involving growth differentiation of hematopoietic cells.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 171**

5 Preferred polypeptides encoded by this gene comprise the following amino acid sequences: ALQLAFYPDAVEEWLEENVHPSLQRLQXLLQDLSEVSAPP (SEQ ID NO:734); and/or CHPPALAGTLLRTPEGRAHARGLLLEAGGA (SEQ ID NO:735). Polynucleotides encoding such polypeptides are also provided. The protein product of this gene shares sequence homology with metallothionines. Thus, polypeptide encoded  
10 by this gene are expected to have metallothionine activity, such activities are known in the art and described elsewhere herein.

This gene is expressed primarily in kidney cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
15 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases of the kidney including cancer and renal dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected  
20 in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the  
25 disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 404 as residues: Ser-47 to Gln-52.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases of the kidney including kidney failure.  
30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 172**

This gene is expressed primarily in 12 week old early stage human.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
35 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing embryo, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 405 as residues: Gln-31 to Thr-43, Gly-51 to Ser-58, Pro-65 to Pro-72.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of developmental problems with fetal tissue. The gene may be involved in vital organ development in the early stage, especially hematopoiesis, cardiovascular system, and neural development.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 173**

The translation product of this gene shares sequence homology with TGN38, an integral membrane protein previously shown to be predominantly localized to the trans-Golgi network (TGN) of cells.

This gene is expressed primarily in developing embryo and to a lesser extent in cancer tissues including lymphoma, endometrial, prostate and colon.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental abnormalities and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 406 as residues: His-65 to Ser-72, Pro-82 to Gly-91, Pro-98 to Glu-118, Ser-126 to Gly-166, Pro-180 to Asp-188, Tyr-209 to Lys-214, Gln-220 to Leu-228.

The tissue distribution and homology to an integral membrane protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for

diagnosis of cancers and developmental abnormalities where aberrant expression relates to an abnormality.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 174**

5       The translation product of this gene shares sequence homology with a dnaJ heat shock protein from *E. coli* which is allelic to sec63, a gene that affects transit of nascent secretory proteins across the endoplasmic reticulum in yeast.

      This gene is expressed primarily in Hodgkin's lymphoma and to a lesser extent in testes.

10       Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification  
15 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to  
20 the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 407 as residues: Thr-13 to Trp-21, Arg-74 to Asp-81.

      The tissue distribution and homology to dnaJ indicates that polynucleotides and  
25 polypeptides corresponding to this gene are useful as a diagnostic for cancer including Hodgkin's lymphoma.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 175**

      This gene is expressed primarily in endothelial cells and to a lesser extent in  
30 bone marrow stromal cells.

      Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, diseases involving angiogenic abnormalities including diabetic  
35 retinopathy, macular degeneration, and other diseases including arteriosclerosis and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell

type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for treating diseases where an increase or decrease in angiogenesis is indicated and as a factor in the wound healing process.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 176**

The translation product of this gene shares sequence homology with MAT8 (mouse) which is thought to be important in regulating chloride conductance in cells (particularly in the breast) by modulating the response mediated by cAMP and protein kinase C to extracellular signals.

This gene is expressed primarily in amniotic cells and hematopoietic cells including macrophages, Neutrophils, T cells, TNF induced aortic endothelium and to a lesser extent in testes, TNF induced epithelial cells, and smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, inflammatory responses mediated by T cells, macrophages, and/or neutrophils particularly those involving TNF, and also cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 409 as residues: Thr-19 to Ala-33, Leu-54 to Asp-82, Pro-89 to Ala-97, Pro-100 to Lys-125, Ser-127 to Phe-135, Gly-164 to Leu-169, Cys-173 to Arg-178.

The tissue distribution and homology to mat-8 indicates that polynucleotides and polypeptides corresponding to this gene are useful for modifying inflammatory

responses to cytokines such as TNF and thus modifying the duration and/or severity of inflammation. Polynucleotides and polypeptides derived from this gene are thought to be useful in the diagnosis and treatment of cancer.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 177

This gene is expressed primarily in endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, vascular restenosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating diseases associated with vascular response to injury such as vascular restenosis following angioplasty..

## FEATURES OF PROTEIN ENCODED BY GENE NO: 178

One embodiment of the claimed invention comprises:

MRPDWKAGAGPGGPPQKPAPSSQRKPPARPSAAAAIAVAAAEERRLRQRN  
RLRLEEDKPAVERCLEELVFGDVENEDALLRRLRGPRVQEHEDSGDSEVENEAKGNFPPQKKPV  
WVDEEDEDEEMVDMMNRRFRKDMMNASESKLSKDNLKKRLKEEFQHAMG  
GVPWAETTKRKTSSDDESEDEDDLLQRTGNFISTSTSLPRGILKMKNQC  
HANAERPTVARISICAVPSRCTDCDGCWD (SEQ ID NO:737); or  
CLEELVFGDVENEDALLRRLRGPRVQEHEDSGDSEVENEAKGNFPPQKKPV  
WVDEEDEDEEMVDMMNRRFRKDMMNASESKLSKDNLKKRLKEEFQHAMG  
GVPWAETTKRKTSSDDESEDEDDLLQRTGNFISTSTSLPRGILKMKNQC  
HANAERPTVARISICAVPSRCTDCDGC (SEQ ID NO: 738). LKEKIVRSFEVSPDGS  
FLLINGIAGYLHLLAMKTKELIGSMKINGRVAASTFSSDSKKVYASSGDGEVYV  
WDVNSRKCLNRFVDEGSLYGLSIATSRNGQYVACGSNCGVVNIYNQDSCLOE  
TNPKPIKAIMNLVTGVTSLTFNPTTEILAIASEKMKEAVRLVHLPSCTVFSNFPVI  
KNKNISHVHTMDFSPRSGYFALGNEKGKALMYRLHHYSDF (SEQ ID NO:739);



and/or KINGRVAASTFSSDSKKVYASSGDGEVYVWDVNSRKCLNRFVDEGSL  
YGLSIATSRNGQYVACGSNCGVVNIYNQDSCLQETNPKPIKAIMNLVTGVTSLT  
FNPTTEILAIASEKMKEAVRLVHLPSCTVFSNFPVIKKNKISHVHTMDFSPRSG  
YFALGNEKGKAL (SEQ ID NO:740).

5 This gene is expressed primarily in epididymus and endometrial tumors and to a lesser extent in T cell lymphoma and cell lines derived from colon cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, tumors of the reproductive organs including testis and endometrial cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 411 as residues: Ser-67 to Lys-72, Val-87 to Leu-93, Tyr-128 to Pro-141, Asp-204 to Gly-210.

The tissue distribution indicates that the protein products of this gene are useful for treating tumors of the endometrium or epithelial tumors of the reproductive system.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 179

Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

MRILQLILLALATGLVGGETRIIKGFECKLHSQPWQAALFEKTRLLCGATLIAPR  
WLLTAAHCLKPRYIVHLGQHNLQKEEGCEQTRTATESFPHPGFNNSLPNKDH  
30 RNDIMLVKMASPV SITWAVRPLTLSSRCVTAGTSCSFPAGAARPDPSYACLT  
DAPTSPSLSTRSVRTPTPATSQTPWCVPACRKGARTPARVTPGALWSVTSLFKA  
LSPGARIRVRSPESLVSTRKSANMWTGSRRR (SEQ ID NO:741); ETRIIKGFEC  
KLHSQPWQAALFEKTRLLCGATLIAPRWLLTAAHCLKPRYIVHLGQHNLQKEE  
GCEQTRTATESFPHPGFNNSLPNKDHRNDIMLVKMASPV SITWAVRPLTLSSR  
35 CVTAGTSCSFPAGAARPDPSYACLTCDAPTSPSLSTRSVRTPTPATSQTPWCVP  
ACRKGARTPARVTPGALWSVTSLFKALSPGARIRVRSPESLVSTRKSANMWTG

SRRR (SEQ ID NO:742); or CKLHSQPWQAALFEKTRLLCGATLIAPRWLLT  
AAHCLKPRYIVHLGQHNLQKEEGCEQTRTATESFPHPGFNS

(SEQ ID NO:743). The translation product of this gene shares sequence homology  
with neuropsin a novel serine protease which is thought to be important in modulating  
extracellular signaling pathways in the brain. Owing to the structural similarity to other  
serine proteases the protein products of this gene are expected to have serine protease  
activity which may be assayed by methods known in the art and described elsewhere  
herein.

This gene is expressed primarily in endometrial tumor and to a lesser extent in  
colon cancer, benign hypertrophic prostate, and thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions, which include, but are  
not limited to, cancers of the endometrium or colon and benign hypertrophy of the  
prostate. Similarly, polypeptides and antibodies directed to these polypeptides are  
useful in providing immunological probes for differential identification of the tissue(s)  
or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
the urogenital or reproductive systems, expression of this gene at significantly higher or  
lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded  
tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or  
another tissue or cell sample taken from an individual having such a disorder, relative to  
the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
fluid from an individual not having the disorder. Preferred epitopes include those  
comprising a sequence shown in SEQ ID NO: 412 as residues: Gly-12 to Ser-22, Pro-  
34 to Ser-53.

The tissue distribution and homology to serine proteases indicates that  
polynucleotides and polypeptides corresponding to this gene are useful for diagnosing  
or treating hyperproliferative disorders such as cancer of the endometrium or colon and  
hyperplasia of the prostate.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 180

Preferred polypeptide encoded by this gene comprise the following amino acid  
sequence: VLQGRYFSPILEMRRLRPEGXXNLPGGSSRAQKEPRQDLTLVLWPHC  
PHFAMTRS YVPTKQCMVQGSFYCIFKGPVQNW C (SEQ ID NO:744).

Polynucleotides encoding such polypeptide are also provided.

This gene is expressed primarily in fetal brain

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, identifying and expanding stem cells in the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for detecting and expanding stem cell populations in the (or of the) central nervous system.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 181**

This gene is expressed primarily in early stage human brain and a stromal cell line.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, developmental abnormalities of the CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 414 as residues: Gln-42 to Gln-47, Gln-54 to Pro-60.

The tissue distribution indicates that the protein products of this gene play a role in the development of the central nervous system. Therefore this gene and its products

are useful for diagnosing or treating developmental abnormalities of the central nervous system.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 182

5 Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

MPIIDQVNPELHDFMQSAEVTIFALSWLITWFGHVLSDFRHVVRLYDF  
 FLACHPLMPIYFAAVIVLYREQEVLDCDCDMASVHHLLSQIPQDLPYETLISRXE  
 TFLFSFHPNLLGRPLNSKLRGRQPLLSKTLSTWHQPSRGLIWCCGSGXRGLL  
 10 RPEDRTKDVLTKPRTNRFVKLAVMGLTVALGAAALAVVKSALWAPKFQLQL  
 FP (SEQ ID NO:745); or CPEFFIPATLPCPFVFAFTSEASSRAYLTQRGPGGLAQ  
 NLMPLPVGFWMGSLPPPWCWRKWVSEACSCFC (SEQ ID NO:746) These  
 polypeptides are structurally similar to various TGF-beta family members. Thus, this  
 polypeptide is expected to have a variety of activities in the modulation of cell growth  
 15 and proliferation.

This gene is expressed primarily in osteoclastoma, microvascular endothelium, and bone marrow derived cell lines.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, hematological diseases particularly involving aberrant proliferation of stem cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
 25 the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 30 individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 415 as residues: Ser-33 to Ala-39.

The tissue distribution indicates that the protein products of this gene is useful for treating disorders of the progenitors of the immune system. Applications include in vivo expansion of progenitor cells, ex vivo expansion of progenitor cells, or the  
 35 treatment of tumors of the circulatory system, such as lymphomas.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 183**

This gene maps to chromosome 17 and therefore, polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 17. In specific embodiments, polypeptides of the invention comprise the sequence:

- 5 GFGSVSAAGRRSGGTWQPVQ (SEQ ID NO:747); PGGLAVGSRWWSRSLT (SEQ ID NO:748); LEPSRQRRPRRRGGTSRPETDQRAKCWRQL (SEQ ID NO:749); and/or VCLRCQNRMEN (SEQ ID NO:750). In further specific embodiments, polypeptides of the invention comprise the sequence: MAACTARRPGR GQPLVVPVADXGPVAKAALCAAXAGAFSPASTTTTTRHLSSNRNRPPEGKVLETV
- 10 GVFEVPKQNGKYETGQLFLHSIFGYRGVVLFPWQARLXDRDVASAAPEKAEN PAGHGSKEVKGKTHTYQVLIDARDCPHISQRSQTEAVTFLANHDDSRALYAIP GLDYVSHEDILPYTSTDQVPIQHELPERFLLYDQTKAPPFVARETLRAWQEKNH PWLELSDVHRETTENIRVTVIPFYMGMREAQNSHVYWWRYCIRLENLSDSDVVQ LRERHWRIFSLSGTLETVRGRGVVGREPVLSKEQPAFQYSSHVSLQASSGHMW
- 15 GTFRFERPDGSHFDVRIPPFSLSENKDEKTPPSGLHW (SEQ ID NO:751); MAACTARRPGRGQPLVVPVADXGPVAKAALCAA (SEQ ID NO:752); VLETVGVEVPKQNGKYETGQLFLHSIFGYRGVVL (SEQ ID NO:757); GLDYVSHEDILPYTST (SEQ ID NO:758); DVHRETTENIRVTVIPFYM (SEQ ID NO:759); WWRYCIRLENLSDSDVQLRER (SEQ ID NO:760); and/or PAFQYSS
- 20 HVSLQASSGHMWGTFRFER (SEQ ID NO:761). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in gall bladder, prostate, and fetal brain, and to a lesser extent in a few tumor and fetal tissues.

- Therefore, polynucleotides and polypeptides of the invention are useful as
- 25 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, growth related disorders such as cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders
- 30 of the above tissues or cells, particularly of the prostate, gall bladder, and fetal brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
- 35 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of growth-related disorders, such cancers.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 184

In specific embodiments, polypeptides of the invention comprise the sequence:SLCCPEGAEGC (SEQ ID NO:762) and/or QLKKTTHYDRPCP (SEQ ID NO:763). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 This gene is expressed primarily in stromal cell, tonsil, and glioblastoma and to a lesser extent in some other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are  
15 not limited to, immune and inflammatory disorders and glioblastoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the stromal cells, tonsil, and glioblastoma expression of this gene at significantly higher or lower levels  
20 may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Additionally, it is believed that the  
25 product of this gene regulates pancreatic cell differentiation into beta cells. Accordingly, polynucleotides and polypeptides of the invention are useful in the treatment of insulin-dependent diabetes mellitus and associated conditions e.g. pancreatic hypofunction and the prevention, as well as the treatment of undifferentiated type pancreatic cancers. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 417 as  
30 residues: Pro-27 to Ala-32.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune and inflammatory disorders and glioblastoma.

## 35 FEATURES OF PROTEIN ENCODED BY GENE NO: 185

This gene is expressed primarily in hepatocellular carcinoma and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, liver diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 418 as residues: Gly-32 to Lys-39.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of liver diseases.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 186**

This gene is expressed primarily in hippocampus and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neuronal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hippocampus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuronal disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 187**

This gene is expressed primarily in bone cancer and hippocampus and to a lesser extent in osteoclastoma and other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, bone-related disorders and neuronal diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone, osteoclast, and hippocampus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of bone-related disorders and neuronal diseases.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 188**

This gene maps to chromosome 4 and therefore polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 4.

This gene is expressed primarily in neuronal tissues such as hippocampus, spinal cord, and hypothalamus and to a lesser extent in a few other tissues such as ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neuronal diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuronal disorders.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 189**

This gene maps to chromosome 10, therefore, polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 10.

5 This gene is expressed primarily in neuronal tissues and immune tissues, and to a lesser extent in a few other tissues such as skin tumor, lung etc.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, neuronal and immune-related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuronal and immune-related tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 422 as residues: Pro-19 to Asp-25.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuronal and immune-related disorders.

**25 FEATURES OF PROTEIN ENCODED BY GENE NO: 190**

The translation product of this gene shares sequence homology with human N33, a gene located in a homozygously deleted region of human metastatic prostate cancer which is thought to be important in prevention of prostate cancer. In specific embodiments, polypeptides of the invention comprise the sequence:

30 AQRKKEMVLSEKVSQLEWTKRVPVIRMGDKFRRLVKAPPRNYSVIVMFTA  
LQLHRQCVVCKQADEEFQILANSWRYSSAFTNRIFFAMVDFDEGSDVFQMLNM  
NSAPTFINFPAGKPKRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPPNMA  
ARWRFWCVSVT (SEQ ID NO:765); MVVALLIVCDVPSAS (SEQ ID NO:766);  
AQRKKEMVLSEKVSQLEWTKRVPVIRMGDKF (SEQ  
35 ID:768); RRLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRY  
SSAFTNRIFFA (SEQ ID NO:769); MVDFDEGSDVFQMLNMNSAPTFINFPAGK  
GKP (SEQ ID NO:770); KRGDTYELQVRGFSAEQIARWIADRTDVNIRVIRPPN

(SEQ ID NO:771); and/or YAGPLMLGLLLA VIGGLVYLRRVTWNFSLIKLDGLLQL CVLCLL (SEQ ID NO:772). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in infant adrenal gland prostate cell line and to a lesser extent in a few other tissues like liver, smooth muscle etc.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, prostate cancer and endocrine disorders. Similarly, polypeptides and  
10 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate and adrenal gland, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma,  
15 urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 423 as residues: Pro-34 to Gly-43, Arg-113 to Pro-120.

20 The tissue distribution and homology to N33 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment for prostate cancer and endocrine disorders.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 191**

25 This gene is expressed primarily in T cell and to a lesser extent in fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to  
30 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal  
35 fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue

or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 424 as residues: Trp-3 to Phe-9.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 192**

This gene maps to chromosome 6, therefore, polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 6. Neural activity and neurotrophins induce synaptic remodeling in part by altering gene expression. This gene is believed to be a glycosylphosphatidylinositol-anchored protein encoded by a hippocampal gene and to possess neural activity. This molecule is believed to be expressed in postmitotic-differentiating neurons of the developing nervous system and neuronal structures associated with plasticity in the adult. Message of this gene is believed to be induced by neuronal activity and by the activity-regulated neurotrophins BDNF and NT-3. The product of this gene is believed to stimulate neurite outgrowth and arborization in primary embryonic hippocampal and cortical cultures and to act as a downstream effector of activity-induced neurite outgrowth. In specific embodiments, polypeptides of the invention comprise the sequence: DAVFKGFSDCLLKLGD (SEQ ID NO:773); CQEGAKDMWDKLRKESKNLN (SEQ ID NO:774); VLLVSLAALATWLSF (SEQ ID NO:775); MGLKLNGRYISLILAVQIAYLVQAVR AAGKCDAVFKGFSDCLLKLGD (SEQ ID NO:776); PAAWDDKTNIKTVC TYW EDFHSCVTALTDCQEGAKDMWDKLRKESKNLN IQGSLFELCGSGNGAAGSL LPAFPVLLVSLAALATWLSF (SEQ ID NO:777); and/or MGLKLNGRYISLILAVQIAYLVQAVRAAGKCDAVFKGFSDCLLKLGD SXXXXXPAAWDDKTNIKTVC TYW EDFHSCVTALTDCQEGAKDMWDKLRKESKNLN IQGSLFELCGSGNGAA GSLLPAFPVLLVSLAALATWLSF (SEQ ID NO:778). Polynucleotides encoding this polypeptide are also encompassed by the invention.

This gene is expressed primarily in human placenta, endometrial tumor and tissues of the central nervous system (CNS).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, relating to reproductive disorders, cancers and neurological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and neurological disorders, expression of this gene at significantly higher

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or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 425 as residues: Asp-47 to Asp-63, His-75 to Tyr-80, Pro-83 to Tyr-89.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of reproductive disorders such as endometrial tumors. Expression of this gene in tissues of the CNS and its strong homology to Neuritin suggest that the protein product from this gene may also be used in the treatment and diagnosis of neurological disorders and in the regeneration of neural tissues, e.g., following injury.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 193**

The translation product of this gene shares sequence homology with tenascin which is thought to be important in development. The translation product of this gene is believed to be a ligand of the fibroblast growth factor family. FGF ligand activity is known in the art and can be assayed by methods known in the art and disclosed elsewhere herein.

This gene is expressed primarily in endometrial tumors, and other types of tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 426 as residues: Gly-29 to Glu-34, Arg-71 to Arg-76, Thr-176 to Cys-182, Gly-184 to Glu-199.

The tissue distribution and homology to tenascin indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancers.

**5 FEATURES OF PROTEIN ENCODED BY GENE NO: 194**

In specific embodiments, polypeptides of the invention comprise the sequence: MNSAAGFSHLDRRERVVLKLGESFEKQPRCASTLC (SEQ ID NO:779).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal human lung and neutrophils.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, lung development and respiratory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes  
15 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual  
20 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal lung and neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis  
25 and treatment of lung and immunity related diseases, for example, lung cancer, viral, fungal or bacterial infections (e.g. lesions caused by tuberculosis), inflammation (e.g. pneumonia), metabolic lesions etc.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 195**

30 This gene is expressed primarily in breast lymph node.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immunal disorders. Similarly, polypeptides and antibodies directed to  
35 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at

significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immunal disorders.

#### 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 196

This gene maps to chromosome 5 and accordingly, polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 5. The translation product of this gene shares sequence homology with human M-phase phosphoprotein 4 which is thought to be important in phosphorylation and signal transduction processes. In

15 specific embodiments, polypeptides of the invention comprise the sequence:

TIYPTEELQAVQKIVSITERALKLVSD (SEQ ID NO:780); RALKGVLRV  
 GVLAKGLLLRGDRNVNLVLLC (SEQ ID NO:781); ALAALRHAKWFQARAN  
 GLQSCVHILRLDLCQRVPTWS (SEQ ID NO:782); GDALRRVFECISSGIL (SEQ  
 ID NO:783); LAFRQIHKVLGMDPLP (SEQ ID NO:784); and/or TIYPTEELQAVQ  
 20 KIVSITERALKLVSDSLSEHEKNKNKEGDDKKEGGKDRALKGVLRVGVLAGK  
 LLLRGDRNVNLVLLCSEKPSKTLISRIAENLPKQLAVISPEKYDIKCAVSEAAIIL  
 NSCVEPKMQVTITLTSPHIREENMREGDVTSGMVKDPPDVLDRQKCLDALAALR  
 HAKWFQARANGLQSCVHILRLDLCQRVPTWSDFPSWAMELLVEKAISSASSP  
 QSPGDALRRVFECISSGILKGSPGLLDPCCKDPFDTLATMTDQQREDITSSAQFA  
 25 LRLLAFRQIHKVLGMDPLPQMSQRFNIHNNRKRRRSDSGVDGFEGGKKDKK  
 DYDNF (SEQ ID NO:785). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

This gene is expressed primarily in Human Hippocampus and to a lesser extent in Prostate, Human Frontal Cortex.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, disorders related to reproductive system and nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
 35 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system and nervous system, expression of this gene at significantly higher or lower

levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to human M-phase phosphoprotein 4 indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of reproductive and nervous system disorders.

#### 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 197

In specific embodiments, polypeptides of the invention comprise the sequence: MGSQHSAAARPSSCRRKQEDDRDG (SEQ ID NO:786); LLAEREQEEAIAQFPYVEFTGRDSITCLTC (SEQ ID NO:787); and/or QGTGYIPTEQVNELVALIPHSQRLRPQRTKQYV (SEQ ID NO:788).

15 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in Human Primary Breast Cancer and to a lesser extent in Human Adult Spleen, Hodgkin's Lymphoma I, Salivary Gland.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, cancer and immunal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 430 as residues: Ser-126 to Gly-138.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and immunal disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 198**

This gene is expressed primarily in monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, blood cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of blood cell disorders.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 199**

This gene is expressed primarily in Human Ovary and Synovia and to a lesser extent in Human 8 Week Whole Embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, reproductive and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and developmental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of reproductive and developmental disorders.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 200**

This gene maps to chromosome 8 and therefore polynucleotides of the invention can be used in linkage analysis as a marker for chromosome 8. The translation product  
5 of this gene shares limited sequence homology with collagen proline rich domain.

This gene is expressed primarily in CNS.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are  
10 not limited to, neurological diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g.,  
15 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 433 as residues:  
20 Pro-35 to Asp-41.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurological diseases.

**25 FEATURES OF PROTEIN ENCODED BY GENE NO: 201**

Translation product of this gene shares homology with a mammalian histone H1a protein. One embodiment for this gene is the polypeptide fragments comprising the following amino acid sequence: ARLNVGRESLKREMLKSQGVKVS E SPMGAR  
HSSWPEGAAFCCKVQGAQM QFP PRR (SEQ ID NO:789); ARLNVGRESLKR  
30 EML (SEQ ID NO:790); LKSQGVKVS E SPMGARHSSW (SEQ ID NO:791);  
AFCKKVQGAQM QFP PRR (SEQ ID NO:792). An additional embodiment is the polynucleotide fragments encoding these polypeptide (See Accession No. pirlS24178) fragments.

This gene is expressed primarily in neutrophils.

35 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are

not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at

5 significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in vital immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such

15 as AIDS, and leukemia.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 202**

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as

20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

25 tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level

30 in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for

35 immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 203**

This gene is expressed primarily in Neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, infectious disorders, immune disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For  
10 a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
15 the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 436 as residues: Thr-31 to Lys-36.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of infectious  
20 disorders, immune disorders, and cancers. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
25 and/or immunotherapy targets for the above listed tumors and tissues.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 204**

This gene maps to chromosome 16 and therefore polynucleotides of the invention can be used in linkage analysis as markers for chromosome 16. The  
30 translation product of this gene shares sequence homology with lactate dehydrogenase which is thought to be important in lactate metabolism.

This gene is expressed primarily in human tonsils and to a lesser extent in Spleen, and Neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, immune disorders, infectious disorders, and cancers. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune disorders, infectious disorders, and cancers, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 437 as residues: Gly-7 to Ser-12.

The tissue distribution and homology to lactate dehydrogenase gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders, infectious disorders, and cancers.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 205**

The translation product of this gene shares sequence homology with Gcap1 protein which is developmentally regulated in brain.

This gene is expressed primarily in placenta and endometrial tumor and to a lesser extent in several other tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions, which include, but are not limited to, vasculogenesis/angiogenesis and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system and tumors, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to Gcap1 protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorder or dysfunction of vascular system of tumorigenesis.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 206**

In specific embodiments, polypeptides of the invention comprise the sequence  
 MPYAQWLAENDRFEEAQKAFHKAGRQREA (SEQ ID NO:799);  
 VQVLEQLTNNAVAESRFNDAAYYYWMLSMQCLDIAQD (SEQ ID NO:794);  
 5 PAQKDTMLGKFYHFQRLAELYHGYHAIHRHTEDP (SEQ ID NO: 795);  
 FSVHRPETLFNISRFLHSLPKDTPSGISKVKILFT (SEQ ID NO:800);  
 LAKQSKALGAYRLARHAYDKLRGLYIP (SEQ ID NO:796); ARFQKSIELG  
 TLIRAKPFHDSEELVPLCYRCSTNN (SEQ ID NO: 797); and/or PLLNNLGNVC  
 INCRQPFIFSASSYDVLHLVEFYLEEGITDEEAISLIDLEVLRPKRDDRQLEICKQQ  
 10 LPDSCG (SEQ ID NO:798). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

This gene is expressed primarily in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 15 biological sample and for diagnosis of diseases and conditions, which include, but are  
 not limited to, male reproductive and endocrine disorders. Similarly, polypeptides and  
 antibodies directed to these polypeptides are useful in providing immunological probes  
 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 of the above tissues or cells, particularly of the reproductive and endocrine systems,  
 20 expression of this gene at significantly higher or lower levels may be routinely detected  
 in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum,  
 plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from  
 an individual having such a disorder, relative to the standard gene expression level, i.e.,  
 the expression level in healthy tissue or bodily fluid from an individual not having the  
 25 disorder.

The tissue distribution indicates that polynucleotides and polypeptides  
 corresponding to this gene are useful for treatment of male reproductive and endocrine  
 disorders.

**30 FEATURES OF PROTEIN ENCODED BY GENE NO: 207**

This gene is expressed in fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions, which include, but are  
 35 not limited to, lung diseases such as cystic fibrosis. Similarly, polypeptides and  
 antibodies directed to these polypeptides are useful in providing immunological probes  
 for differential identification of the tissue(s) or cell type(s). For a number of disorders

of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual  
5 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 440 as residues: Tyr-49 to Cys-54.

The tissue distribution indicates that polynucleotides and polypeptides  
10 corresponding to this gene are useful for detection and treatment of disorders associated with developing lungs particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of lung tumors since the gene may be involved in the regulation of cell division,  
15 particularly since it is expressed in fetal tissue. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO. X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO. Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HLHDS67	97979 03/27/97	Uni-ZAP XR	11	2526	427	2526	458	458	234	1	30	31	30
2	HLHDZ58	97979 03/27/97	Uni-ZAP XR	12	1131	1	1131	129	129	235	1	14	15	115
3	HLMMJ13	97979 03/27/97	Lambda ZAP II	13	941	39	941	62	62	236	1	44	45	102
3	HLMMJ13	97979 03/27/97	Lambda ZAP II	218	941	39	941	245	245	441	1	35	36	41
4	HLTEI25	97979 03/27/97	Uni-ZAP XR	14	843	1	843	155	155	237	1	19	20	42
5	HMSJX24	97979 03/27/97	Uni-ZAP XR	15	1018	1	1018	90	90	238	1	18	19	36
6	HNFEED65	97979 03/27/97	Uni-ZAP XR	16	661	1	661	76	76	239	1	28	29	127
7	HNHDX07	97979 03/27/97	Uni-ZAP XR	17	553	1	553	106	106	240	1	23	24	66
8	HNHGC82	97979 03/27/97	Uni-ZAP XR	18	869	1	869	101	101	241	1	21	22	68
9	HNHGO09	97979 03/27/97	Uni-ZAP XR	19	959	1	959	176	176	242	1	21	22	44
10	HOUBEI8	97979 03/27/97	Uni-ZAP XR	20	1446	1	1446	101	101	243	1	27	28	50
11	HOUDL69	97979 03/27/97	Uni-ZAP XR	21	1471	579	1460	692	692	244	1	31	32	42

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
12	HPMF171	97979 03/27/97	Uni-ZAP XR	22	1402	242	1402	401	245	1	32	33	60
13	HPMGQ55	97979 03/27/97	Uni-ZAP XR	23	1047	1	1047	164	246	1	26	27	35
14	HPQAC69	97979 03/27/97	Lambda ZAP II	24	990	1	988	82	247	1	20	21	37
15	HPTBB03	97979 03/27/97	Uni-ZAP XR	25	1208	350	1173	398	248	1	29	30	210
16	HPTWA66	97979 03/27/97	pBluescript	26	1922	1381	1922	24	249	1	33	34	547
16	HPTWA66	97979 03/27/97	pBluescript	219	575	1	575	148	442	1	22	23	65
17	HPTWC08	97979 03/27/97	pBluescript	27	1951	1422	1874	219	250	1	19	20	299
18	HRGCZ46	97979 03/27/97	Uni-ZAP XR	28	3989	2635	3989	2748	251	1	16	17	39
19	HSADVU34	97979 03/27/97	Uni-ZAP XR	29	3735	2966	3735	272	252	1	30	31	594
19	HSADVU34	97979 03/27/97	Uni-ZAP XR	220	3018	1929	3018	26	443	1	1	2	156
20	HSDFW61	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	30	1667	59	1625	138	253	1	32	33	130
21	HSDGP60	97974 04/04/97	Uni-ZAP XR	31	1408	1	1408	285	254	1			20



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		209080 05/29/97												
22	HSQA155	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	32	2031	1273	2031	1285	1285	255	1	29	30	30
23	HSQE084	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	33	971	13	971	91	91	256	1	19	20	218
23	HSQE084	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	221	968	8	968	86	86	444	1	20	21	56
24	HSXAM05	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	34	1792	369	1792	470	470	257	1	26	27	49
25	HSXAS67	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	35	896	1	896	96	96	258	1	32	33	121
26	HTDAF28	97974 04/04/97 209080 05/29/97	pSport1	36	912	1	912	38	38	259	1	22	23	87
27	HTEGQ64	97974	Uni-ZAP XR	37	1382	67	1382	271	271	260	1			25

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		04/04/97 209080 05/29/97												
28	HTGEU09	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	38	872	1	872	74	74	261	1	18	19	28
29	HTOAM21	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	39	812	1	812	41	41	262	1	30	31	43
30	HTPBW79	209511 12/03/97	Uni-ZAP XR	40	1515	118	1507	302	302	263	1	24	25	362
30	HTSEV09	97974 04/04/97 209080 05/29/97	pBluescript	222	1404	1	1265	92	92	445	1	19	20	415
31	HTPCD40	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	41	704	22	704		117	264	1	18	19	127
32	HTWBY48	97974 04/04/97 209080 05/29/97	pSport1	42	1094	1	1094	32	32	265	1	34	35	53
33	HTWC146	97974 04/04/97	pSport1	43	1821	892	1647	56	56	266	1	26	27	28

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT of AA of Signal Pep	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		209080 05/29/97												
34	HTXG175	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	44	1024	30	1024		167	267	1	20	21	25
35	HWTFB59	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	45	983	779	983	85	85	268	1	30	31	221
35	HWTFB59	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	223	707	488	707	514	514	446	1	41	42	64
36	HADA E74	97974 04/04/97 209080 05/29/97	pSport1	46	2421	664	1587	710	710	269	1			2
37	HAGFB60	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	47	840	1	840	97	97	270	1	30	31	48
38	HATEF60	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	48	2432	1193	2246	1491	1491	271	1	17	18	51
39	HBMSN25	97974	Uni-ZAP XR	49	1742	1165	1742	1207	1207	272	1	23	24	31

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
40	HCDAR68	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	50	1487	181	1455	325	325	273	1	35	36	56
41	HCE3J79	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	51	1328	251	1328	525	525	274	1			21
42	HMDAN54	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	52	1856	725	1853	928	928	275	1	33	34	50
43	HCECA49	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	53	1558	310	1408	393	393	276	1			1
44	HCEEC15	97974 04/04/97 209080 05/29/97	Uni-ZAP XR	54	948	1	948	9	9	277	1	23	24	65
45	HCESF40	97974 04/04/97 209080 05/29/97	pBluescript	55	990	99	990	193	193	278	1	32	33	256

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
45	HCESF40	97974 04/04/97 209080 05/29/97	pBluescript	224	1384	99	1384	193	193	447	1	32	33	205
46	HCFMV39	97974 04/04/97 209080 05/29/97	pSport1	56	1603	1	1296	96	96	279	1	29	30	102
47	HCMSSX86	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	57	1052	5	786	12	12	280	1	28	29	32
48	HCNAP62	97975 04/04/97 209081 05/29/97	Lambda ZAP II	58	814	1	558	93	93	281	1	22	23	42
49	HCRAF32	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	59	1215	257	1215		356	282	1	19	20	20
50	HCUDC07	97975 04/04/97 209081 05/29/97	ZAP Express	60	478	1	478	147	147	283	1	36	37	69
51	HCWBB42	97975 04/04/97 209081	ZAP Express	61	618	1	618	212	212	284	1	35	36	74

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
52	HDTAB05	97975 04/04/97 209081	PCMVSPORT 2.0	62	751	1	751	257	257	285	1	21	22	32
53	HE2AV74	97975 04/04/97 209081	Uni-ZAP XR	63	780	283	780		433	286	1			16
54	HE2AY71	97975 04/04/97 209081	Uni-ZAP XR	64	588	21	588	169	169	287	1			16
55	HE2GS36	97975 04/04/97 209081	Uni-ZAP XR	65	774	272	774	445	445	288	1			37
56	HE2OF09	97975 04/04/97 209081	Uni-ZAP XR	66	1866	1313	1866	1596	1596	289	1			11
57	HE6EU50	97975 04/04/97 209081	Uni-ZAP XR	67	1152	117	686	237	237	290	1	20	21	34
58	HE9HU17	97975 04/04/97	Uni-ZAP XR	68	2483	1577	2448	1620	1620	291	1			14

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
59	HE9ND48	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	69	536	1	536	83	83	292	1	36	37	43
60	HEBBW11	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	70	865	647	865		388	293	1	30	31	135
61	HELDY74	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	71	932	1	932	201	201	294	1	17	18	33
62	HEMAE80	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	72	996	1	945	12	12	295	1	24	25	136
63	HFEBAB88	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	73	785	464	785	356	356	296	1	29	30	57
64	HFGAB89	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	74	1069	196	1047	295	295	297	1	32	33	34
65	HFVHY45	97975	pBluescript	75	831	1	831		89	298	1	30	31	76

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
66	HGBAJ93	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	76	590	1	590	233	233	299	1	38	39	94
67	HGBBQ69	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	77	1274	1	1273	105	105	300	1	24	25	43
68	HHFCF08	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	78	1133	4	1042	175	175	301	1	23	24	30
69	HHFHJ59	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	79	661	1	661	192	192	302	1	29	30	112
70	HHFHR32	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	80	1378	1	1378		358	303	1			13
71	HHGCN69	97975 04/04/97 209081 05/29/97	Lambda ZAP II	81	1440	298	1440	532	532	304	1	23	24	34



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
72	HHGDOI3	97975 04/04/97 209081 05/29/97	Lambda ZAP II	82	1381	766	1371	993	305	1	23	24	34
73	HHPF63	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	83	1706	182	1644	257	306	1	24	25	81
74	HHSEG23	97976 04/04/97	Uni-ZAP XR	84	573	1	573	160	307	1	18	19	71
75	HIPAV06	97976 04/04/97	Uni-ZAP XR	85	684	199	684	323	308	1	27	28	33
76	HKIXL73	97976 04/04/97	pBluescript	86	1036	591	1036	690	309	1	32	33	114
77	HKMNC43	97976 04/04/97	pBluescript	87	908	1	908	139	310	1	18	19	108
78	HMEJE31	97976 04/04/97	Lambda ZAP II	88	655	1	655	165	311	1	33	34	64
79	HMSK35	97976 04/04/97	Uni-ZAP XR	89	1102	1	1102	228	312	1	26	27	49
80	HNFAE54	97976 04/04/97	Uni-ZAP XR	90	1533	665	1518	347	313	1	26	27	293
81	HNFIH45	97976 04/04/97	Uni-ZAP XR	91	575	1	575	275	314	1	30	31	67
82	HNGBT31	97976 04/04/97	Uni-ZAP XR	92	639	1	639	224	315	1	28	29	104

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
83	HNGIN60	97976 04/04/97	Uni-ZAP XR	93	744.	1	744	225	225	316	1	43	44	70
84	HNGJG84	97976 04/04/97	Uni-ZAP XR	94	526	1	526	268	268	317	1	29	30	38
85	HNHDW42	97976 04/04/97	Uni-ZAP XR	95	426	1	426	168	168	318	1	28	29	71
86	HNHFL57	97976 04/04/97	Uni-ZAP XR	96	844	1	844	98	98	319	1	25	26	61
87	HOGAR52	97977 04/04/97 209082 05/29/97	pcMVSPORT 2.0	97	1985	453	1985	533	533	320	1	17	18	285
88	HOSBZ55	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	98	1416	69	1416	246	246	321	1	32	33	54
89	HOSDI92	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	99	1935	141	772		274	322	1	20	21	58
90	HPBCU51	97977 04/04/97 209082 05/29/97	pBluescript SK-	100	599	1	599	86	86	323	1	27	28	119
91	HPCAL49	97977 04/04/97 209082	Uni-ZAP XR	101	784	1	784		280	324	1	18	19	43

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
92	HPFCRI3	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	102	1035	602	1035	859	859	325	1	32	33	58
93	HPHAC83	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	103	2218	840	2182	1035	1035	326	1	17	18	17
94	HPMBQ32	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	104	1351	1	1351	18	18	327	1	23	24	86
95	HPWAN23	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	105	2066	51	2052	270	270	328	1	29	30	537
95	HPWAN23	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	226	2057	1	1954	220	220	449	1	29	30	315
96	HRDFB85	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	106	1705	23	1697	233	233	329	1	21	22	201
97	HRGBR28	97977 04/04/97	Uni-ZAP XR	107	1167	611	1167	53	53	330	1	1	2	263

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		209082 05/29/97												
98	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	108	1907	151	1432	353	353	331	1	23	24	260
98	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	227	2084	335	2084	537	537	450	1	19	20	23
99	HSPAH56	97977 04/04/97 209082 05/29/97	pSport1	109	611	1	576	229	229	332	1	25	26	47
100	HE8EU04	209746 04/07/98	Uni-ZAP XR	110	2632	294	2632	337	337	333	1	25	26	333
100	HSXBT86	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	228	2143	53	1096	235	235	451	1			9
101	HSXCS62	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	111	2249	1	1953	90	90	334	1	18	19	199
102	HTEFU09	97977 04/04/97 209082	Uni-ZAP XR	112	2198	228	2158	400	400	335	1			23

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of First AA of Signal Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
103	HTKEM35	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	113	1043	40	1043	320	320	336	1	20	21	142
104	HTGEP89	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	114	703	1	703	285	285	337	1	29	30	94
105	HTGEW91	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	115	3684	526	1338	584	584	338	1	24	25	37
106	HTOEY16	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	116	1965	127	1915	202	202	339	1	27	28	38
107	HTPCN79	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	117	503	1	503		1	340	1	7	8	70
108	HTSGM54	97977 04/04/97 209082 05/29/97	pBluescript	118	1133	316	1069		423	341	1	12	13	84
109	HTSHE40	97977 04/04/97	pBluescript	119	1101	118	956	218	218	342	1	31	32	89

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of First AA of Signal Pep	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		209082 05/29/97												
110	HTWAF58	97977 04/04/97 209082 05/29/97	Lambda ZAP II	120	282	1	282	137	137	343	1	25	26	48
111	HTWBY29	97977 04/04/97 209082 05/29/97	pSport1	121	2635	1593	2489	1654	1654	344	1	25	26	55
112	HUKFC71	209007 04/28/97 209083 05/29/97	Lambda ZAP II	122	994	1	932	272	345	1	15	16	221	
113	HCE3Q10	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	123	1542	1	1542	143	143	346	1	25	26	63
114	HCEVR60	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	124	1390	82	1390	127	127	347	1	32	33	153
115	HDTAW95	209007 04/28/97 209083 05/29/97	pcMVSPORT 2.0	125	1288	412	1288	571	571	348	1			16
116	HE6EL90	209007	Uni-ZAP XR	126	1517	1	1452	243	243	349	1			9

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		04/28/97 209083 05/29/97												
117	HELBUE29	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	127	1073	198	1073		776	350	1			13
118	HERAH36	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	128	300	155	300	202	202	351	1			17
119	HFXBW82	209007 04/28/97 209083 05/29/97	Lambda ZAP II	129	1275	1	1275	56	56	352	1	23	24	61
120	HHPTD20	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	130	472	51	472		243	353	1			32
121	HIBED17	209007 04/28/97 209083 05/29/97	Other	131	1950	284	1927	395	395	354	1	72	73	245
122	HLTER03	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	132	990	1	990	78	78	355	1	22	23	34

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
123	HOABL56	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	133	1720	565	1720	660	660	356	1	18	19	21
124	HPMC192	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	134	705	28	705	106	106	357	1	28	29	98
125	HPWAZ95	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	135	323	1	323	88	88	358	1	27	28	78
126	HRGBR18	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	136	582	1	582		16	359	1	17	18	30
127	HSUBW09	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	137	1021	1	1021	153	153	360	1	32	33	56
128	HUKCO64	209007 04/28/97 209083 05/29/97	Lambda ZAP II	138	1777	439	1777		521	361	1			2
129	H6EAA53	209007 04/28/97 209083	Uni-ZAP XR	139	643	303	643		313	362	1	7	8	31



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO. X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO. Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
130	HAGAI11	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	140	1220	1	1220		127	363	1	16	17	27
131	HAGAO39	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	141	721	1	721		415	364	1			14
132	HALSK07	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	142	1468	125	1468	210	210	365	1	29	30	33
133	HALSQ59	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	143	300	4	300	101	101	366	1	22	23	66
134	HAIBP89	unknown 05/18/98	Uni-ZAP XR	144	2243	173	2243	311	311	367	1	27	28	317
134	HBCGB91	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	229	1025	409	1025	624	624	452	1	20	21	25
135	HBM1D81	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	145	1082	163	1082	357	357	368	1			30

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
136	HBXGK12	209008 04/28/97 209084 05/29/97	ZAP Express	146	4313	1153	4313	1313	1313	369	1	18	19	42
137	HFKFJ07	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	147	1183	1	1183	149	149	370	1	41	42	254
138	HCQA140	209008 04/28/97 209084 05/29/97	Lambda ZAP II	148	734	1	734	285	285	371	1			19
139	HCWHZ24	209008 04/28/97 209084 05/29/97	ZAP Express	149	1405	1	1405	108	108	372	1	34	35	63
140	HE2GT20	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	150	2890	1178	2890	1178	1178	373	1	31	32	39
141	HEBEY43	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	151	2399	1181	2399	1265	1265	374	1	30	31	34
142	HFCB37	209008 04/28/97 209084	Uni-ZAP XR	152	802	352	802		487	375	1			10

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
143	HFTCT67	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	153	461	24	461	145	145	376	1	37	38	63
144	HGLAM46	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	154	2388	818	2388	648	648	377	1			18
145	HHGBR15	209008 04/28/97 209084 05/29/97	Lambda ZAP II	155	642	322	642	400	400	378	1			4
146	HJAAU36	209008 04/28/97 209084 05/29/97	pBluescript SK-	156	1251	583	1251		933	379	1	16	17	16
147	HUSIT49	209008 04/28/97 209084 05/29/97	pSport1	157	2127	247	2127	383	383	380	1	47	48	83
148	HKLAB16	209008 04/28/97 209084 05/29/97	Lambda ZAP II	158	1625	817	1625	1012	1012	381	1	18	19	20
149	HLMMU76	209008 04/28/97	Lambda ZAP II	159	1687	1307	1687	1296	1296	382	1	28	29	28

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		209084 05/29/97												
150	HMSKQ35	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	160	1842	172	1463	319	319	383	1	30	31	33
151	HNHED86	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	161	770	1	770	30	30	384	1	31	32	46
152	HNHEJ88	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	162	519	1	519	242	242	385	1	17	18	24
153	HNHFQ63	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	163	753	1	753	164	164	386	1	17	18	67
154	HOECU83	209009 04/28/97	Uni-ZAP XR	164	1400	189	1400		508	387	1	22	23	33
155	HPTRC15	209009 04/28/97	pBluescript	165	2153	594	2153		611	388	1			13
156	HSKCP69	209009 04/28/97	Uni-ZAP XR	166	1251	219	1120			389	1			
156	HSKCP69	209009 04/28/97	Uni-ZAP XR	230	1250	223	1250	393	393	453	1	32	33	171
157	H6EAE26	209009	Uni-ZAP XR	167	882	48	882	155	155	390	1	33	34	153

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
158	HAGBX03	209009 04/28/97	Uni-ZAP XR	168	1208	1	1208	182	182	391	1			8
159	HAGDQ47	209009 04/28/97	Uni-ZAP XR	169	1307	1	1307	44	44	392	1	22	23	60
160	HAICP19	209009 04/28/97	Uni-ZAP XR	170	1624	89	1483	128	128	393	1	18	19	446
161	HAUAE83	209009 04/28/97	Uni-ZAP XR	171	2003	889	2003	1080	1080	394	1			23
162	HBHAD12	209009 04/28/97	Uni-ZAP XR	172	786	1	786		176	395	1	17	18	23
163	HBMTY28	209009 04/28/97	Uni-ZAP XR	173	1758	962	1758	1184	1184	396	1	27	28	34
164	HBMPV04	209009 04/28/97	Uni-ZAP XR	174	888	330	862		546	397	1			2
165	HCDDB78	209009 04/28/97	Uni-ZAP XR	175	2379	750	2379	901	901	398	1	18	19	24
166	HCEQA68	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	176	1348	1	1348	12	12	399	1	28	29	78
167	HCEZS40	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	177	1502	178	1502	315	315	400	1			20
168	HCFNF11	209010	pSport1	178	1637	26	1607	152	152	401	1	44	45	257

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
		04/28/97 209085 05/29/97												
169	HCRBL20	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	179	2911	1103	2858	192	192	402	1	32	33	424
169	HCRBL20	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	231	1811	20	1811	93	93	454	1	36	37	95
170	HCUBL62	209010 04/28/97 209085 05/29/97	ZAP Express	180	519	1	519	57	57	403	1	28	29	32
171	HDSAP81	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	181	968	320	968	476	476	404	1	27	28	79
172	HE2CT29	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	182	1128	1	1128	111	111	405	1	26	27	94
173	HE8MG65	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	183	2276	48	2276	88	88	406	1	37	38	257

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO. X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO. Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
173	HE8MG65	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	232	2271	56	2232	79	79	455	1	43	44	170
174	HE9FB42	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	184	2500	76	1693	518	518	407	1	1	2	623
175	HEMAM41	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	185	1337	60	1328	175	175	408	1	39	40	190
175	HEMAM41	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	233	1338	33	1327	175	175	456	1	32	33	91
176	HEMCV19	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	186	941	33	931	79	79	409	1	23	24	178
177	HEMDX17	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	187	654	1	654	137	137	410	1			13
178	HETAR54	209010 04/28/97 209085	Uni-ZAP XR	188	1848	454	1848	948	948	411	1	14	15	232

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
179	HETBX14	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	189	1146	157	1146		74	412	1	14	15	53
180	HFGAB48	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	190	906	156	906	245	245	413	1	30	31	32
181	HFKFI40	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	191	1941	120	1002	213	213	414	1	18	19	218
182	HFXHN68	209010 04/28/97 209085 05/29/97	Lambda ZAP II	192	2118	777	2118	966	966	415	1	23	24	50
183	HGBFO79	209011 04/28/97	Uni-ZAP XR	193	1538	259	1538	273	273	416	1	23	24	49
184	HGLAM56	209011 04/28/97	Uni-ZAP XR	194	1098	68	1098		185	417	1	28	29	69
185	HHLBA89	209011 04/28/97	pBluescript SK-	195	1001	1	1001	324	324	418	1	25	26	39
186	HHPDW05	209011 04/28/97	Uni-ZAP XR	196	1443	1	1443	246	246	419	1	21	22	21
187	HHPSD37	209011 04/28/97	pBluescript	197	1282	66	1282	171	171	420	1	19	20	37



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
188	HHP5F70	209011 04/28/97	pBluescript	198	951	26	951		162	421	1	16	17	34
189	HHS AK25	209011 04/28/97	Uni-ZAP XR	199	1740	1390	1740	1534	1534	422	1	19	20	31
190	HIASB53	209011 04/28/97	pBluescript	200	1707	401	1195	652	652	423	1	26	27	126
191	HJABZ65	209011 04/28/97	pBluescript SK-	201	779	1	779	23	23	424	1	26	27	68
192	HJPBB39	209011 04/28/97	Uni-ZAP XR	202	1617	188	1605	182	182	425	1	28	29	91
193	HLHSK94	209011 04/28/97	pBluescript	203	1974	1	1794	112	112	426	1	26	27	379
194	HLHTC70	209011 04/28/97	pBluescript	204	1057	229	1057	365	365	427	1	23	24	22
195	HLMIW92	209011 04/28/97	Lambda ZAP II	205	721	1	721	244	244	428	1	25	26	46
196	HLTCY93	209011 04/28/97	Uni-ZAP XR	206	2465	988	2465	1225	1225	429	1			4
197	HLTDB65	209011 04/28/97	Uni-ZAP XR	207	1480	1	1480		371	430	1	15	16	143
198	HMSHM43	209011 04/28/97	Uni-ZAP XR	208	872	1	872	35	35	431	1	18	19	36
199	HMSHQ24	209011 04/28/97	Uni-ZAP XR	209	1779	16	1779	148	148	432	1	24	25	36
200	HNFAH08	209011 04/28/97	Uni-ZAP XR	210	2110	592	2110	611	611	433	1	18	19	191

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
201	HNGAO10	209011 04/28/97	Uni-ZAP XR	211	938	1	938	107	107	434	1	27	28	30
202	HNGBE45	209011 04/28/97	Uni-ZAP XR	212	1551	1	1551	114	114	435	1	21	22	100
203	HNHAZ16	209011 04/28/97	Uni-ZAP XR	213	997	1	997	202	202	436	1	24	25	36
204	HNHCM59	209011 04/28/97	Uni-ZAP XR	214	1496	1	1132		165	437	1	28	29	41
205	HOSFM22	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	215	1308	501	1308		809	438	1			1
206	HPHAC88	97977 04/04/97 209082 05/29/97	Uni-ZAP XR	216	1705	384	1705	549	549	439	1	23	24	24
207	HCDEO95	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	217	999	608	999	273	273	440	1	22	23	54

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table I. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

- 5       The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources  
10       using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

### Signal Sequences

- 15       Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1  
20       indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

- 25       In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results  
30       shown in Table 1.

- As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., +  
35       or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

#### 10 Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

15 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

25 As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are:

35 Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions,

5 interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be  
10 determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and  
15 subject sequences are either both nucleotide sequences or both amino acid sequences.

The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window  
20 Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity.

25 For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of  
30 the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the  
subject sequence, which are not matched/aligned with the query sequence, are  
35 considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.



For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

**Polynucleotide and Polypeptide Fragments**

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the

carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Particularly, N-terminal deletions of the polypeptide of the present invention can be described by the general formula m-p, where p is the total number of amino acids in the polypeptide and m is an integer from 2 to (p-1), and where both of these integers (m & p) correspond to the position of the amino acid residue identified in SEQ ID NO:Y.

Moreover, C-terminal deletions of the polypeptide of the present invention can also be described by the general formula 1-n, where n is an integer from 2 to (p-1), and again where these integers (n & p) correspond to the position of the amino acid residue identified in SEQ ID NO:Y.

The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:Y, where m and n are integers as described above.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

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### **Epitopes & Antibodies**

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an

epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

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### Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the

polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

5        Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

10        Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final  
15        preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

20        Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG)  
25        can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

30        Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the  
35        fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D.

Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein.

Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

#### 15 Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance



genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein

after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

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### Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

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Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

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Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

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Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

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For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are

more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model

systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of

unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

### Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic

resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human  
5 subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The  
10 Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene  
15 expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to  
20 supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired  
25 response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such  
30 as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also  
be used to raise antibodies, which in turn are used to measure protein expression from a  
35 recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

### **Biological Activities**

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

### **Immune Activity**

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can

decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

5 A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation,  
10 differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis,  
15 glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune  
20 inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

25 A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The  
30 administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may  
35 inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic



shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

### **Hyperproliferative Disorders**

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

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### **Infectious Disease**

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases

may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

- 5           Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

- 25           Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS

related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas.

These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal

or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase  
5 regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue  
10 regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and  
15 peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease,  
20 Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

### **Chemotaxis**

25 A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular  
30 trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system  
disorder by increasing the number of cells targeted to a particular location in the body.  
35 For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

5

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit  
10 (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural  
15 or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

20 Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing  
25 the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results  
30 in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate  
35 compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

5 All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

10 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with  
15 a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

#### **Other Activities**

20 A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic  
25 surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian  
30 rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a  
35 food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

**Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

5 Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

10 Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

15 Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

20 Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide  
30 sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer  
35 as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method



comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

5 Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of  
10 comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95%  
15 identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

20 The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

25 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous  
30 nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

35 The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95%

identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

### Examples

#### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
laflmid BA	plafmid BA
pSport1	pSport1
pCMVSPORT 2.0	pCMVSPORT 2.0
pCMVSPORT 3.0	pCMVSPORT 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1

Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS-. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported.

The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).)

The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $MgCl_2$ , 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.



This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then  
5 be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA  
10 synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

#### **Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR  
20 using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

#### **Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by,  
25 among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is  
30 then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's  
protocol number PT1190-1. Following hybridization and washing, the blots are  
35 mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

**Example 4: Chromosomal Mapping of the Polynucleotides**

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

**Example 5: Bacterial Expression of a Polypeptide**

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance ( $Amp^r$ ), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance ( $Kan^r$ ). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG

(Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA

insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

- 5       The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

**Example 6: Purification of a Polypeptide from an Inclusion Body**

- 10       The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

- 15       Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

- 20       The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

- 25       The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

- 30       Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area

(e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

### **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus**

#### **Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., *Proc. Natl. Acad. Sci. USA* 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm

tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- 5        After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.)
- 10       After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in
- 15       35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

- To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection
- 20       ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins
- 25       in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

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30       **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates

the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the



polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

**Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCC
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCTCTTCCCCCAAAC
CAAGGACACCCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGT
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
```

AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG  
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC  
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT  
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT  
5 GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA  
GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG  
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA  
GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC  
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGC  
10 GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

**Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of  
15 the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

20 In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell  
25 Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at  
30 about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the  
present invention; however, it is preferable to employ the parent myeloma cell line  
35 (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as

described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

#### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a

working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of  $\text{CaCl}_2$  (anhyd); 0.00130 mg/L  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ; 0.050 mg/L of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ; 0.417 mg/L of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ; 311.80 mg/L of KCl; 28.64 mg/L of  $\text{MgCl}_2$ ; 48.84 mg/L of  $\text{MgSO}_4$ ; 6995.50 mg/L of NaCl; 2400.0 mg/L of  $\text{NaHCO}_3$ ; 62.50 mg/L of  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ; 71.02 mg/L of  $\text{Na}_2\text{HPO}_4$ ; .4320 mg/L of  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ ; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of

Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

**Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATs</u>	<u>GAS(elements) or ISRE</u>
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3	
	<u>gp130 family</u>						
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
	<u>g-C family</u>						
20	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
25	<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS
30	<u>Growth hormone family</u>						
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
35	<u>Receptor Tyrosine Kinases</u>						
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)
40							



To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTCCCCGAAATCTAGATTCCCCGAAATGATTCCCCG  
AAATGATTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGTCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTCCCCGAAATCTAGATTCCCCGAAATGATTCCCCGAAATG  
ATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCC  
CTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGC  
CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGC  
CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTT  
TGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

**Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

- 5 During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

- 10 On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

- 15 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

- 20 After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

- 25 The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

- 30 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

**Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells.

- 5 Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

- 10 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

- 15 Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37°C for 45 min.

- 20 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

- 25 These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

- 30 Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.
-

**Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine

growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- $\kappa$ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- $\kappa$ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF-  $\kappa$ B is retained in the cytoplasm with I- $\kappa$ B (Inhibitor  $\kappa$ B). However, upon stimulation, I-  $\kappa$ B is phosphorylated and degraded, causing NF-  $\kappa$ B to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF-  $\kappa$ B include IL-2, IL-6, GM-CSF, ICAM-1 and class I-MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating

diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:  
 5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC  
 TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC  
 ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCA  
 TCCCGCCCCTAACTCCGCCCAGTTCCGCCCATCTCCGCCCCATGGCTGACT  
 AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTC  
 CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:  
 3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15  $\mu$ l of 2.5x dilution buffer into Optiplates containing 35  $\mu$ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50  $\mu$ l Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50  $\mu$ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6



23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

**Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50  $\mu$ l of 12  $\mu$ g/ml fluo-3 is added to each well. The plate is incubated at 37°C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100  $\mu$ l of buffer.

5 For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4  $\mu$ l of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100  
10  $\mu$ l/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200  $\mu$ l, followed by an aspiration step to 100  $\mu$ l final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the  
15 following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50  $\mu$ l. Increased emission at 530-nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

20

#### **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase  
25 RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

30 Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-  
35 receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a

biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

- 5        The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2+</sub> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the
- 10 components gently and preincubate the reaction mix at 30°C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

- Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction
- 15 mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as
- 20 above.

- Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of
- 25 tyrosine kinase activity.

#### **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

- As a potential alternative and/or complement to the assay of protein tyrosine
- 30 kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase,
- 35 Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other

phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

#### **Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30

seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies).

The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

5 PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

10 Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

15 Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. 20 et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated 25 disease.

#### **Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

30 A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

35 For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

#### **Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1  $\mu\text{g/kg/day}$  to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1  $\mu\text{g/kg/hour}$  to about 50  $\mu\text{g/kg/hour}$ , either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules.

10 Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008;

20 U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.



The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

**Example 24: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form.

- 5 Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

- 10 For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

**Example 25: Method of Treating Increased Levels of the Polypeptide**

- 15 Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

- 20 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

**Example 26: Method of Treatment Using Gene Therapy**

- 25 One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is  
30 turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

5 pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

10 The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to  
15 transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is  
20 then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media,  
25 containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is  
30 required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

**Example 27: Method of Treatment Using Gene Therapy - In Vivo**

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide of the present invention. A polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the encoded polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) *Cardiovasc. Res.* 35(3):470-479, Chao J et al. (1997) *Pharmacol. Res.* 35(6):517-522, Wolff J.A. (1997) *Neuromuscul. Disord.* 7(5):314-318, Schwartz B. et al. (1996) *Gene Ther.* 3(5):405-411, Tsurumi Y. et al. (1996) *Circulation* 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs of the present invention may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). These polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) *Ann. NY Acad. Sci.* 772:126-139 and Abdallah B. et al. (1995) *Biol. Cell* 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs of the present invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the present invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for the polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with

liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA of the present invention.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference.

## Sequence Listing

### (1) GENERAL INFORMATION:

5 (i) APPLICANT: Human Genome Sciences, Inc., et al.

(ii) TITLE OF INVENTION: 207 Human Secreted Proteins

10 (iii) NUMBER OF SEQUENCES: 800

(iv) CORRESPONDENCE ADDRESS:

15 (A) ADDRESSEE: Human Genome Sciences, Inc.

(B) STREET: 9410 Key West Avenue

20 (C) CITY: Rockville

(D) STATE: Maryland

25 (E) COUNTRY: USA

(F) ZIP: 20850

30 (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette, 3.50 inch, 1.4Mb storage

35 (B) COMPUTER: HP Vectra 486/33

(C) OPERATING SYSTEM: MSDOS version 6.2

(D) SOFTWARE: ASCII Text

40

(vi) CURRENT APPLICATION DATA:

45 (A) APPLICATION NUMBER:

(B) FILING DATE:

(C) CLASSIFICATION:

50

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(vii) PRIOR APPLICATION DATA:

55 (A) APPLICATION NUMBER:

(B) FILING DATE:

343

(B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

	GGCACGAGCC GNCACGGGCA GCGCCCCATA GCGCCAGGGA CCCCCTGGCA GCGGGAGCCG	60
	CGGGTCGAGG TTATGGATCC AGCGGGCGGC CCCCGGGCG TGCTCCCGG GCCCTGCCGG	120
10	TGNTGGTGC TGCTGAACCC GCGCGGCGGC AAGGGCAAGG CCTTGCAGCT CTTCCGAGT	180
	CACGTGCAGC CCCTTTTGGC TGAGGCTGAA ATCTCCTTCA CGCTGATGCT CACTGAGCGG	240
15	CGGAACCACG CGCGGGARCT GGTGCGGTGC GAGGAGCTGG GCCGCTGGRA CGCTCTGGTG	300
	GTCATGTYTG GAGACGGGCT GATGCACGAG GTGGTGAACG GGCTTCATGG AGCGGCCTGA	360
	CTGGGAGACC GCCATCCAGA AGCCCCGTGT TAGCCTCCCA GCAGGCTCTG GCAACGCSCT	420
20	GGCAGCTTCC TTRAACCAT TATGCTGGCTA TRAGCAGGTC ACCAATGAAG ACCTCCTGAC	480
	CAACTGCACG CTATTGCTGT GCCGCCGGCT GCTGTCACCC ATGAACCTGC TGTCTCTGCA	540
25	CACGGCTTCG GGGCTGCGCC TCTTCTCTGT GCTCAGCCTG GCCTGGGGCT TCATTGCTGA	600
	TGTGGACCTA GAGAGTGAGA AGTATCGGCG TCTGGGGGAG ATGCGCTTCA CTCTGGGCAC	660
	CTTCCTGCGT CTGGCAGCCC TGCGCACCTA CCGCGGCCGA CTGGCCTACC TCCCTGTAGG	720
30	AAGAGTGGGT TCCAAGACAC CTGCCTCCCC CGTTGTGGTC CAGCAGGGCC CGGTAGATGC	780
	ACACCTTGTG CCACTGGAGG AGCCAGTGCC CTCTCACTGG ACAGTGGTGC CCGACGAGGA	840
35	CTTTGTGCTA GTCTGGCAC TGCTGCACTC GCACCTGGGC AGTGAGATGT TTGCTGCACC	900
	CATGGGCGCG TGTGCAGCTG GCGTCATGCA TCTGTTCTAC GTGCGGGCGG GAGTGTCTCG	960
40	TGCCATGCTG CTGCGCCTCT TCCTGGCCAT GGAGAAGGGC AGGCATATGG AGTATGAATG	1020
	CCCCTACTTG GTATATGTGC CCGTGGTGC CTTCCGCTTG GAGCCCAAGG ATGGGAAAGG	1080
	TGTGTTTGCA GTGGATGGGG AATTGATGGT TAGCGAGGCC GTGCAGGGCC AGGTGCACCC	1140
45	AAACTACTTC TGGATGGTCA GCGGTTGCGT GGAGCCCCCG CCCAGCTGGA AGCCCCAGCA	1200
	GATGCCACCG CCAGAAGAGC CCTTATGACC CCTGGGCCGC GCTGTGCCTT AGTGTCTACT	1260
	TGCAGGACCC TTCTCTCTTC CCTAGGGCTG CAGGGCCTGT CCACAGCTCC TGTGGGGGTG	1320
50	GAGGAGACTC CTCTGGAGAA GGGTGAGAAG GTGGAGGCTA TGCTTTGGGG GGACAGGCCA	1380
	GAATGAAGTC CTGGGTCAGG AGCCAGCTG GCTGGGCCCA GCTGCCTATG TAAGGCCTTC	1440
55	TAGTTTGTTC TGAGACCCCC ACCCCACGAA CCAATCCAA ATAAAGTGAC ATTCCCAAAA	1500
	AAAAAAAAA AAAAAAAAAA ANCCCGNNGG GGG	1533

60



AAAAAAAAA AAAAAAACY GRAGGGGGC CCGGTACCAA TCGCCCTAT AATGA

655

5

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 1102 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

15

TTTTTTTTTTT ACCATTTAAA ATAAATGAA AGTGACCTTC TGTTTATAAA AATCTTTGTC 60  
TGCATCTCTG CTTATTTCTT TAGAAGAGAT TCCAAGAAGC GGTGAGTGAT TTCACGGCAG 120  
20 CAGAGGGTTG GGACATATTA CGGGCGCGGA TCCCTCTTGG AGTGAGATGA CTCTCCGGAG 180  
AGATTTAGTC GTCACCCTCG CGTGTGAGGC TCGGTCACAC CCCAGGGATG TGTCTATCAA 240  
GATGGAAGAT CTTTACACG CTCTTGATTT TGTGGSCTY TTTTCTATT ACTAGTGAGA 300  
25 AKGAACTTT TTATATGATT ATTATCCATC ATAATCCAAC ACAAATTACT GCTTCATGTT 360  
CTTTTACTTT CCTGTGAAGG TTTTAGTGCC TTTTAAAAAT TGCTATATAT TAAGCTTGTT 420  
30 AATACTTCCA TGCTGTATTT GTGGSCATCA RPTTCCCCGG GNACAGGNT GCACATTTTG 480  
CCTTCACACG CTGGGTGGTT TTTATTTTC AMTCTATTT CTCGTTCTTC TATCGTTTTA 540  
TGTTTCAGACG GGTTCCTCCG TGTAGAAAGC AGTTTATGAA GATTTACTTT CGACAGTCTT 600  
35 CTCTCTACTT TCTACAGTGA ATTCTCTGAT GTGTCTGGGA GTTGGGGGT CTGGGTAAGA 660  
RTCTCTCTCT CACCTATTC TCTATTACGA TCCACAGCCT CATGCTTTAT GARATTGGTG 720  
40 GCCGGGARCG GGGGAGATT GCGGATCCCC CAAGCCAGAC TTTATCCCCC TATCCCTGCC 780  
TCTGGATCCC ACGTACAGGC CTGGGAATC CCTGTGGGTA GGGGCCAATG GTCTCGCACT 840  
CTCACCTGTA CCCCAGGGCT GGCACAGGAT GGTCAAGGAG AGAGGCTGCC CAAGCGCATC 900  
45 CYTCTGGTGT CCCCTGACA CGCTCCAAA GTGAGCAGGT AGGTTTCAAC AGCCCCACGT 960  
TGCAGGTGGG AGATGAAGCT CAGGGTGGAG ACCAGTATCT CACAGTTCTC TTTGCATGGC 1020  
50 CGGGTACTTG TTAGTCAACT GATCAAGTGA AAATCTAGC CCCAGAGGCA GGAGAATCCG 1080  
GAACAAAATT AAACCAGCCA GG 1102

55

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:

- 60 (A) LENGTH: 1533 base pairs

523.

Tyr Lys Asp Phe Tyr Phe Ser Ile Ser Leu His Leu Pro Thr Leu Leu  
                             85                            90                            95

5 Phe Xaa Xaa Xaa Phe Val Phe Ser Leu Leu Pro Pro  
                             100                            105

10 (2) INFORMATION FOR SEQ ID NO: 311:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 65 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 311:

Met Cys Ser Pro Ser Leu Ser Ser Ser Pro Pro Pro Leu Leu Gln Val  
     1                            5                            10                            15

20 Phe Phe Phe Phe Phe Phe Ser Pro His Trp Ala Ala Lys Val Val Pro  
                             20                            25                            30

25 Gln Trp Lys Xaa Arg His Pro Gln Val Ser Ser Gln Leu Leu Cys  
                             35                            40                            45

Phe Leu Arg Val Asn Cys Gln Phe Leu Phe Leu Gln Glu Ile Leu Phe  
     50                            55                            60

30 Xaa  
     65

35 (2) INFORMATION FOR SEQ ID NO: 312:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 50 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 312:

Met Cys Leu Ser Arg Trp Lys Ile Phe Tyr Thr Leu Leu Ile Leu Phe  
     1                            5                            10                            15

45 Xaa Xaa Phe Ser Ile Thr Ser Glu Xaa Glu Thr Phe Tyr Met Ile Ile  
                             20                            25                            30

50 Ile His His Asn Pro Thr Gln Ile Thr Ala Ser Cys Ser Phe Thr Phe  
                             35                            40                            45

Leu Xaa  
     50

55

(2) INFORMATION FOR SEQ ID NO: 313:

(i) SEQUENCE CHARACTERISTICS:

60 (A) LENGTH: 293 amino acids

524

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 313:

5 Met Glu Arg Pro Asp Trp Glu Thr Ala Ile Gln Lys Pro Leu Cys Ser  
     1                    5                    10                    15  
 Leu Pro Ala Gly Ser Gly Asn Ala Leu Ala Ala Ser Leu Asn His Tyr  
                     20                    25                    30  
 10 Ala Gly Tyr Xaa Gln Val Thr Asn Glu Asp Leu Leu Thr Asn Cys Thr  
                     35                    40                    45  
 Leu Leu Leu Cys Arg Arg Leu Leu Ser Pro Met Asn Leu Leu Ser Leu  
 15       50                    55                    60  
 His Thr Ala Ser Gly Leu Arg Leu Phe Ser Val Leu Ser Leu Ala Trp  
       65                    70                    75                    80  
 20 Gly Phe Ile Ala Asp Val Asp Leu Glu Ser Glu Lys Tyr Arg Arg Leu  
                     85                    90                    95  
 Gly Glu Met Arg Phe Thr Leu Gly Thr Phe Leu Arg Leu Ala Ala Leu  
                     100                    105                    110  
 25 Arg Thr Tyr Arg Gly Arg Leu Ala Tyr Leu Pro Val Gly Arg Val Gly  
                     115                    120                    125  
 Ser Lys Thr Pro Ala Ser Pro Val Val Val Gln Gln Gly Pro Val Asp  
 30       130                    135                    140  
 Ala His Leu Val Pro Leu Glu Glu Pro Val Pro Ser His Trp Thr Val  
       145                    150                    155                    160  
 35 Val Pro Asp Glu Asp Phe Val Leu Val Leu Ala Leu Leu His Ser His  
                     165                    170                    175  
 Leu Gly Ser Glu Met Phe Ala Ala Pro Met Gly Arg Cys Ala Ala Gly  
                     180                    185                    190  
 40 Val Met His Leu Phe Tyr Val Arg Ala Gly Val Ser Arg Ala Met Leu  
                     195                    200                    205  
 Leu Arg Leu Phe Leu Ala Met Glu Lys Gly Arg His Met Glu Tyr Glu  
 45       210                    215                    220  
 Cys Pro Tyr Leu Val Tyr Val Pro Val Val Ala Phe Arg Leu Glu Pro  
       225                    230                    235                    240  
 50 Lys Asp Gly Lys Gly Val Phe Ala Val Asp Gly Glu Leu Met Val Ser  
                     245                    250                    255  
 Glu Ala Val Gln Gly Gln Val His Pro Asn Tyr Phe Trp Met Val Ser  
                     260                    265                    270  
 55 Gly Cys Val Glu Pro Pro Pro Ser Trp Lys Pro Gln Gln Met Pro Pro  
                     275                    280                    285  
 Pro Glu Glu Pro Leu  
 60       290

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>161</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <u>---</u></span>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>March 27, 1997</u>	Accession Number <u>97979</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <u>---</u></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application <p style="text-align: center;">Michael Smith Genetic Socialist PCT Applications</p>	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer <p style="text-align: center;">04 JUN 1998</p>	Authorized officer

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>162</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>April 4, 1997</u>	Accession Number <u>97974</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")     	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>162</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 29, 1997</u>	Accession Number <u>209080</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")          	
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>164</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <u>---</u>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>December 3, 1997</u>	Accession Number <u>209511</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <u>---</u>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")     	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>167</u> . line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>April 4, 1997</u>	Accession Number <u>97975</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")          	
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>171</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>April 4, 1997</u>	Accession Number <u>97976</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>172</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>April 4, 1997</u>	Accession Number <u>97977</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>172</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) <p>10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p>	
Date of deposit <u>May 29, 1997</u>	Accession Number <u>209082</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")          	
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>176</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>April 28, 1997</u>	Accession Number <u>209007</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (If the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>176</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 29, 1997</u>	Accession Number <u>209083</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")          	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>179</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit April 28, 1997	Accession Number 209008
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>179</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 29, 1997</u>	Accession Number <u>209084</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")     	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit April 28, 1997	Accession Number 209010
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")          	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 29, 1997</u>	Accession Number <u>209085</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")          	
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>182</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <div style="text-align: center;">American Type Culture Collection</div>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit April 28, 1997	Accession Number 209009
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>186</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit <u>April 28, 1997</u>	Accession Number <u>209011</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")	

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>174</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>April 7, 1998</u>	Accession Number <u>209746</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (If the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit")     	

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***What Is Claimed Is:***

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:
  - (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
  - (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

- (g) a variant of SEQ ID NO:Y;
  - (h) an allelic variant of SEQ ID NO:Y; or
  - (i) a species homologue of the SEQ ID NO:Y.
12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
15. A method of making an isolated polypeptide comprising:
- (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
  - (b) recovering said polypeptide.
16. The polypeptide produced by claim 15.
17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.
18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
  - (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.
19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
  - (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.



20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 22.

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